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Problems Associated With Routine Immunizations

C. ARDEN MILLER*

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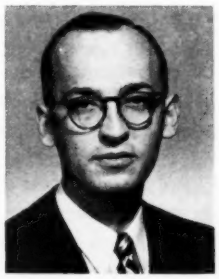

C. ARDEN MILLER

New information relating to the prevention of disease by immunization demands that from time to time we appraise and modify existing practices and concepts. New biologicals are developed; new reactions are recognized; new epidemiologic patterns brought about in part by immunization practices are documented; and new vaccines against hitherto uncontrolled disease are added to immunization schedules.

This article considers these developments as they relate to diphtheria, tetanus, pertussis, smallpox and poliomyelitis—the diseases against which immunizing prophylaxis is most generally practiced in the United States. It includes a discussion of certain problems common to all or several immunizing procedures, and a separate consideration of the prophylaxis of each disease. A summation is presented in the form of a suggested immunization schedule.

Combined Vaccines

In view of the extensive use of biologicals incorporating diphtheria and tetanus toxoids and pertussis vaccine (DPT antigen) in this country for immunizing young children, it is surprising that all doubts have not been dispelled as to the wisdom of using such combined vaccines rather than consecutive courses of single antigens. The combined vaccine offers the obvious advantages of a decreased number of injections and protection against all three diseases at an earlier age than is possible with single antigens. Possible disadvantages arise from claims that two or more antigens given concurrently may interfere with each other, inducing a less than adequate antibody response against one of them. As yet, a

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controlled field trial extensive enough to discount these claims completely has not been conducted, but such a study is in progress in Great Britain. Many past studies relating to this problem are no longer applicable. Some biologicals in current use are of greater potency and purity than those used previously. It is reasonable to expect that these factors may influence the antibody response.

Most immunization procedures have come into use without benefit of elaborate field trials. Exceptions are vaccinations against poliomyelitis and pertussis. Judgments drawn from pilot studies, and critical appraisal, often following prolonged uncontrolled use in the field, form the basis for most of our practices. Such judgments show overwhelmingly that combined antigens compare favorably with single antigens in safety and effectiveness. In fact, there is evidence that the pertussis vaccine in combined DPT antigen potentiates the antibody response to diphtheria and tetanus toxoids, and that the latter do not interfere with or "crowd out" the pertussis antibody response when the antigens are "in balance."[1]

A definitive answer to the problems of combined immunization, as we may expect from the British study, is eagerly sought now that the possibility of including poliomyelitis vaccine with DPT is being discussed. We may anticipate the answer on the basis of the statement by Edsall:[2] "One may conclude, quite tentatively, since the subject is not closed—that the antibody-forming capacity of normal man is capable of assimilating a considerably larger load than it is likely to have imposed on it under any but the most extreme circumstances." Experience in immunizing troops during World War II indicates that four or more antigens administered in combined form may not be an "extreme circumstance."

There does not appear to be an increase in the number or severity of reactions to vaccine mixtures as compared with those following antigens given separately.[3,4]

Use of Adjuvants

Certain oils or minerals which enhance the antibody-provoking properties of antigens when mixed with them are known as adjuvants. Alum has been the adjuvant used most commonly in clinical practice. Initially it was reported that precipitation with alum and washing with saline increased the antigenicity of diphtheria toxoid a hundredfold as compared with untreated, or fluid, toxoid.[5] The means by which adjuvants accomplish this potentiation is not entirely known. The belief that they cause retention of the vaccine at the site of injection and slow release over a period of time for prolonged antigenic stimulation may oversimplify the situation. With some adjuvants the injection site can be extirpated as soon as one-half hour after the injection without any substantial reduction in antibody response.[2]

The advantages of alum-precipitated toxoids and vaccines over fluid preparations have been summarized as follows: more prolonged antitoxic immunity, greater effectiveness as immunizers against pertussis in early infancy, and less likelihood of systemic reactions by virtue of lower protein content and slower absorption.[6] The disadvantages are a greater delay between injection and immunologic protection and a higher incidence of local reactions.[6]

Two mineral carriers, aluminum phosphate and aluminum hydroxide, are even more effective as adjuvants than alum, and produce fewer reactions.[7,8] A single injection of aluminum phosphate-adsorbed diphtheria toxoid induced five to six times as much antitoxin in guinea pigs as a similar amount of the best quality alum-precipitated toxoid.[9] In a series of 852 injections of aluminum phosphate-adsorbed DPT, local and systemic reactions were less frequent and milder than in a previous series of 652 injections of alum-precipitated DPT studied by the same author.[7] It seems entirely possible that with newer, more potent toxoids and more effective, less irritating adjuvants the disadvantages cited for vaccines with mineral carriers will be vitiated.

Age of Immunization

Until recently, most authorities advocated deferring immunization until at least six months of age, on the basis that younger in-

fants were less able to produce antibodies and that the passively acquired (transplacental) circulating antibodies interfered with development of active immunity. Osborn and associates,[10] using single injections of potent diphtheria and tetanus toxoids, demonstrated that infants as young as two weeks of age produce antibody titers higher than the levels generally considered as protective, albeit somewhat lower than levels achieved by infants two months of age and older. The presence of passively acquired circulating antibody depressed the level of active immunity but not appreciably below protective levels in most instances. Where there was interference with antibody response, the giving of a second injection of toxoid (as certainly would be done in practice) resulted in a prompt and high antibody rise.[11]

An interesting side light to these studies was the observation that premature infants behave immunologically like full-term infants. Regardless of the birth weight, it was the duration of extra-uterine life that was the deciding factor in antibody responses, the antigenic stimulus and preinoculation immune state being the same.

There are good reasons to begin and complete the primary course of immunizations as early as possible. Very young infants have undesirable reactions to immunizations less commonly than do older ones. Further, the morbidity and mortality rates of some diseases are highest in the first year of life. From 50 to 70 per cent of the deaths from pertussis occur at this age. Obviously, unless we complete the primary course of immunization very early, some infants will succumb to a preventable disease. It is now common practice to give the first immunization at the six week checkup and to complete the full course of primary immunization, including smallpox vaccination, by the age of six months.

Diphtheria

The immunizing agent used for diphtheria prophylaxis is a toxoid, the formalin-treated soluble exotoxin of *Corynebacterium diphtheriae*. When properly administered, this agent induces active immunity in nearly all persons. The Schick test will ascertain which persons are immune, but it is not completely infallible.

Public health records of morbidity and mortality provide dramatic evidence of the value of diphtheria prophylaxis. For example, in Massachusetts the total number of reported cases of diphtheria fell from around 8000 annually in the early 1920s to only 31 in 1953.[12] The decrease coincided with the advent of extensive immunization programs.

Control of diphtheria depends on achieving group immunity as well as individual immunity. A sufficiently high proportion of the population must be immune at a given time so that the diphtheria bacillus (nearly always present in large populations) passes from one susceptible person to another with great difficulty. It is estimated that 70 per cent of the population must be immune for effective control of the disease and prevention of spread from carriers and sporadic cases.

It is distinctly possible that our excellent record of diphtheria control is in jeopardy, because in many communities the proportion of immune individuals has fallen far below 70 per cent. We face the interesting paradox of having produced a predominantly susceptible population as a result of immunization programs. When diphtheria was rampant, as high a proportion of the adult population as 90 per cent had acquired a natural immunity. The natural booster effect of a large reservoir of infection maintained this level of immunity. Today a great many children are immunized in infancy. This immunity often is not maintained either through booster injections or through natural exposure; five years after primary immunization, one-third of the persons, not having received booster injections, again are susceptible to diphtheria as indicated by the Schick test. Persons who never have been artificially immunized are frequently susceptible throughout their adult life because of the decreased opportunity to acquire natural immunity. As a consequence, we have a population of predominantly immune youngsters and susceptible adults. In Massachusetts, for example, 15 per cent of children under 10 years of age are susceptible; 55 per cent of persons over 20 years of age are susceptible, and this

latter figure is as high as 90 per cent in some areas. This represents a reversal of the immune status 30 years ago.[12] The consequence of this might be predicted: "Although adult cases have dropped fourfold from the previous decades to the past decade, deaths have decreased but slightly, and an ominous rise in adult fatality is noted. . . . For higher age groups case fatalities began to decrease, but have taken a sharp rise in the last decade. Late years have shown a conspicuous number of diphtheria cases in old people."[12]

Yet another consequence of the situation in which the adult population is predominantly nonimmune is that fewer newborn infants have acquired passive (transplacental) immunity. This makes immunization in the early weeks of life more desirable and also more effective.

Procedure—Infants and children under 10 years of age should receive two or three intramuscular injections of 0.5 ml. diphtheria toxoid with a mineral carrier at monthly intervals. In practice, usually three injections of toxoid in mixture with other vaccines are given. If more rapid immunization is desired —e.g., if diphtheria is present in the community—three injections of *fluid* diphtheria toxoid can be given at 10 day intervals. Either regimen constitutes primary immunization. If this is done in infancy, a booster injection (0.2 to 0.5 ml.) is given a year later and thereafter at intervals of three or four years until the age of 10 years. Boosters preferably should be adjuvant toxoid. If rapid antibody recall is desired—e.g., if an immunized person has been exposed to the disease—*fluid* toxoid without adjuvant should be used for the booster.

Sensitivity and severe reactions to diphtheria toxoid are seen occasionally in persons over 10 years of age. For this reason, diphtheria toxoid should not be given to persons over 10 years of age, either alone or in combination with other antigens, without a prior test for sensitivity (Moloney test). This is done by preparing a 1:100 dilution of fluid toxoid and injecting 0.1 ml. intradermally. Erythema and induration 48 hours later indicate sensitivity, and diphtheria toxoid should not be given.

Persons over 10 years of age should be tested by the Schick method every three years. If the result of the test is negative, there is no need for a booster; the test itself serves as a small booster. If the result is positive, indicating susceptibility, a toxoid sensitivity test should be done. If the toxoid sensitivity test gives a negative result, diphtheria toxoid is given. Usually 0.1 ml. is used for the first injection, and then larger doses (0.2 to 0.5 ml.) are given twice, at monthly intervals, if no reaction to the previous injection occurs. It may be convenient to perform the Schick and toxoid sensitivity tests at the same time.

Recent experience with diphtheria indicates the need for maintaining immunity throughout childhood and adult life. Unfortunately, the regimen for immunizing adults against the disease or even for boosting their immunity is sufficiently cumbersome to discourage its widespread use. Edsall and associates[13] recently demonstrated that highly potent diphtheria toxoid in small doses (one flocculating unit contrasted to the 20 to 100 units usually used) adsorbed on aluminum phosphate can induce immunity in nearly all adults and can be given with complete safety (low protein content) without prior testing for sensitivity. This obviates the need for both sensitivity tests and Schick tests. The toxoid can be given every three years routinely, preferably in conjunction with tetanus toxoid. Unless one is certain that he is administering such a pure and potent toxoid, he must follow the more cumbersome procedure. One state laboratory (Massachusetts) now provides the safe potent toxoid for use in adults, and it is hoped that it soon will be available commercially.

Reactions—Reactions to diphtheria toxoid were previously mentioned. Redness, induration, tenderness and pain of varying intensity may persist for several days following injection. Occasionally an encapsulated sac containing sterile pus forms in 7 to 10 days. This sac, termed an "antigenic cyst," may break down and drain, or persist for several weeks as a subcutaneous nodule. In one large series, antigenic cysts developed in slightly more than 2 per cent of persons receiving injections. The cysts are thought to occur more

commonly with alum preparations, when injections are given subcutaneously rather than deep in a muscle, and in persons with a prior immunity to diphtheria.[14]

Systemic reactions consist usually of fever, restlessness and irritability and appear from 48 to 72 hours after inoculations. These reactions probably never are fatal, but in adults a severe generalized illness with high fever and incapacitation may last several days. Young children tolerate diphtheria toxoid very well.

Tetanus

Immunization against tetanus is exceedingly effective and largely devoid of undesirable reactions. Evaluation of its effectiveness is not complicated by subclinical infections or natural immunity. If an individual has antibodies against tetanus, either he acquired them passively by injection (or, in newborns, transplacentally) and the immunity is therefore temporary, or he was artificially immunized.

Ever since World War I, when experience in the British army demonstrated that tetanus antitoxin administered immediately following injury reduced dramatically the incidence of tetanus, this prophylactic precaution has been employed extensively in civilian practice. The precaution is necessary for nonimmunized persons but it does not guarantee that tetanus will not develop. A recent report on 15 patients with tetanus stated that two of them had received 1500 units of tetanus antitoxin shortly after the injury which was presumed to be the site of entry of the tetanus bacillus.[15] Furthermore, half or more of all cases of tetanus occur without an antecedent history of injury or in persons with such trivial injuries that medical care is not sought. Obviously, only active immunity, maintained throughout life, can prevent these cases.

Inasmuch as tetanus reaches its peak incidence between the ages of five and nine years, immunization against it must be completed in early childhood. Active immunization which is maintained periodically and at times of injury with boosters virtually guarantees against tetanus. During World War II, there were only six cases of tetanus in over 2,000,000 recorded wounds among our immunized troops, who usually received a booster injection at the time of injury.[16]

Immunized persons in severe and prolonged shock may not respond to booster injections with a high level of antibody recall. Only in such instances is it advisable to give tetanus antitoxin prophylactically to *immunized* persons, along with a toxoid booster injected at a different site.

Procedure—The antigen used for immunization against tetanus is a toxoid, the formalin-treated soluble exotoxin of *Clostridium tetani.* Primary immunization is achieved by giving two injections of 0.5 ml. of adjuvant toxoid intramuscularly 4 to 12 weeks apart. In infancy, three injections usually are given in combination with diphtheria toxoid and pertussis vaccine.

Booster injections of 0.2 to 0.5 ml. of adjuvant toxoid are given a year after primary immunization and every three years thereafter. An additional booster should be given when an injury occurs. The "wound booster" should be fluid toxoid rather than adjuvant toxoid, because the former agent induces a more rapid antibody recall.

The question arises as to how much time can elapse between primary immunization against tetanus and the giving of a booster for adequate prophylaxis. Experience with persons immunized during World War II shows that there is good antibody recall after 10 years.[17] Although the capacity for rapid antibody recall persists as long as that, protective levels of circulating antibody are not maintained in all persons unless boosters are given more frequently. In some persons the circulating antibody level falls below protective levels three years after primary immunization.[17] Until there is evidence that protection from tetanus depends on something other than the level of circulating antibody, it would seem wise to give a booster every three years.

Reactions—Mild local and systemic symptoms occasionally follow injection of tetanus toxoid, but they are so mild and infrequent that sensitivity tests are unnecessary.

Pertussis

Prophylactic vaccines against whooping

cough have been in use since shortly after the causative agent was isolated. Most vaccines are suspensions of killed *Hemophilus pertussis* organisms. Vaccines have varied in that they were prepared from organisms in different antigenic phases (rough or smooth), cultured in different media, and prepared in different ways. Largely as a result of these variations, estimates of the effectiveness of pertussis immunization have been contradictory at times.

Two recent studies have contributed greatly to knowledge of pertussis immunization. The first is the field trial carried out by the British Medical Research Council. "No controlled studies of this scope and statistical conclusiveness have ever been carried out for any other immunizing procedure," poliomyelitis vaccination not excluded.[2] Among "home exposures" the attack rates in vaccinated children ranged from 7.3 per cent to 30.4 per cent, with varying potencies of the vaccine accounting for the differences. Among the corresponding nonvaccinated groups the attack rates varied from 79.5 to 90.5 per cent. The vaccinated children in whom attacks occurred had milder and less prolonged disease than did the unvaccinated.[18]

The second important development concerns laboratory measures of potency and standardization of vaccine. Until recently, vaccine dosage was determined on the basis of the number of killed organisms injected; 30 to 100 billion killed organisms in divided doses were necessary to confer immunity. However, antigenic potency is related to a number of factors other than the number of organisms. The National Institutes of Health, using a mouse protection test, has established a unit measure of potency. Twelve antigenic units are necessary to confer immunity. Adoption of this unit measure should eliminate the use of weak vaccines and reduce the number of reactions by avoiding excessive dosage.[19]

We cannot dispute the fact that prophylaxis of whooping cough, particularly in infancy, continues to be a necessary public health precaution. During 1954 the number of reported deaths in the United States due to whooping cough was 375, and the actual total almost certainly was higher.

Procedure—Three injections of pertussis vaccine given a month apart and totaling 12 NIH units will confer immunity. The injections are nearly always 0.5 ml. each. Usually the vaccine is precipitated or absorbed by alum or aluminum hydroxide and combined with tetanus and diphtheria toxoids. If rapid immunization is necessary, such as during a local epidemic, either the fluid or plain vaccine may be administered (12 NIH units divided in three equal doses administered at intervals of one week).

A routine booster injection should be given one year after completion of the primary course and again three years later. Booster injections against whooping cough usually are discontinued after four to six years of age. Following intimate exposure or in the presence of a local epidemic, an immunized child less than four years of age should receive a booster injection of 4 NIH units of fluid (plain) vaccine.

Reactions—Reactions are more common among children following injections of pertussis vaccine than following diphtheria or tetanus toxoid injections. With rare exceptions they are not serious enough to interfere with completion of the immunization program. Local reactions usually are mild; but at times a nodule forms, and rarely a draining antigenic cyst develops. Systemic reactions are described in as many as one-third of the vaccinated infants and consist of fever, irritability and anorexia. These symptoms may appear within a few hours and persist as long as 36 hours. The temperature may rise as high as 103° F. Reactions are sufficiently frequent so that many physicians routinely prescribe small doses of aspirin with pertussis immunization.

Encephalitis, with high fever, convulsions, spinal fluid changes, and permanent neurologic sequelae, has been attributed to pertussis vaccination in a few cases. These symptoms usually have their onset within 24 hours after immunization.[20] If they occur, pertussis vaccine should not, of course, be given subsequently. Severe reactions may follow the first dose of vaccine but are more likely to follow the second or third.

Smallpox

Vaccination against smallpox is the only immunization procedure in common use which employs a living organism for an antigen. For this reason, there are certain rare complications against which one must safeguard. Smallpox vaccination has the further distinction of being probably the most effective immunization procedure we have. The antigen is the live vaccinia virus grown on calves' bellies and harvested in the form of vesicular fluid and lymph. The virus has been grown successfully in embryonated eggs and in chick embryo tissue cultures, and these may be desirable sources of virus for vaccine. However, the results with the virus of calf origin have been so salutary that it is doubtful that this technic will be replaced quickly.

Because the vaccine is a living virus, special precautions are required for storage. Sealed glass tubules in which the virus is supplied must be kept at subfreezing temperatures. The large storage chamber of most refrigerators is not cold enough; the vaccine must be kept in the freezing chamber. Attention must be paid to the expiration date; over-age virus should be discarded.

Procedure—The method of vaccination most widely used is the multiple pressure technic. The skin, usually just above the insertion of the deltoid, is prepared with soap and water and swabbed with acetone. The reason for using acetone instead of alcohol is the faster evaporation; antiseptic left on the skin may inactivate the virus and result in an unsuccessful "take." A drop of vaccine is placed on the prepared skin, and the point of a sterile needle held at a 15 degree angle is pressed through the drop into the skin a number of times. The punctures should be confined to an area 2 mm. in diameter. The injection site is allowed to air dry or is blotted dry with sterile cotton. A dressing is not applied, but a clean long-sleeved white shirt should be worn, and changed daily.

Many excellent descriptions and photographs of the various "takes" are available.[21] The most important fact to remember is that a "take" must always result from successful vaccination. Even immune persons who are revaccinated develop accelerated reactions. Failure to develop any reactions is the result of faulty technic either in virus storage or in vaccination.

The optimum age for primary vaccination is during the first year of life. Undesirable complications are less frequent at that age than among older children, and care of the vaccination site is simpler than at more active ages. Most programs for immunization suggest vaccination against smallpox at the fifth or sixth month.* Repeated vaccination is necessary every five or six years and whenever there is increased risk of exposure if over a year has elapsed since the last vaccination.

Complications—Smallpox vaccination is an exceedingly safe procedure; serious complications are rare. Accidental secondary vaccinations sometimes are seen. These may occur when a vaccinated child scratches the inoculation site and then scratches his nose or rubs his eyes. The secondary vaccination develops apace with the primary one. A handkerchief used to blot the injection site and then to wipe brother's nose has been a successful instrument of vaccination.

Widely distributed cutaneous lesions that resemble vaccinoid reactions can occur spontaneously 6 to 14 days after primary vaccination. This complication, called generalized vaccinia, is especially likely if a generalized skin rash such as eczema is present. Generalized vaccinia easily may develop in an unvaccinated child with eczema as a result of exposure to a vaccinated child. The complication is a serious one, at times resembling smallpox itself. In 1947, when 5,000,000 persons in New York City were vaccinated during a one month period, generalized vaccinia developed in 45 persons; 38 had a pre-existing dermatitis, and of these, 28 were not vaccinated but were infected accidentally by contact with vaccinated persons. The two deaths which occur-

*Dr. C. Henry Kempe has collected considerable data on reactions to smallpox vaccination. On the basis of his experience, he believes that the first smallpox vaccination should be done in the second year of life instead of the first when reactions, although less frequent, are apt to be more severe. (Personal communication.)

red among this group of 45 persons were both of babies less than a year of age.[22]

Encephalitis is another serious complication, and it may develop 10 to 13 days after vaccination. Fever, vomiting, convulsions and other signs of encephalitis and meningeal irritation appear. If the patient survives, recovery usually is complete. Among the 5,000,000 persons in New York City who were vaccinated, encephalitis developed in 45; not all cases were proved to be related directly to the vaccination. Four patients died.[22]

Another serious complication is vaccinia gangraenosa, a progressive spread of the primary vaccination to produce extensive local necrosis with heaped-up borders and marginal daughter lesions. It has developed in only a few persons, and all have died after a period of weeks or months except one child who recovered after being treated with hyperimmune vaccinia gamma globulin.[23] This material may be obtained by telephoning or wiring Dr. C. Henry Kempe, Department of Pediatrics, University of Colorado, Denver. One should consider its use for any person suffering generalized vaccinia, vaccinia encephalitis or vaccinia gangraenosa.[23]

Poliomyelitis

The Salk vaccine in current use is a mixture of the three types of poliomyelitis virus rendered noninfectious by formaldehyde. It has been shown that such vaccine, properly prepared and administered, is safe in that it will not transmit poliomyelitis or cause undesirable reactions.[24] It will induce antibody formation in nearly everyone vaccinated,[25] and it will protect a large proportion of such persons from the paralytic form of poliomyelitis.[24] Experience with the vaccine is insufficient to know how long immunity will last, how frequently boosters are needed, if at all, how effective mixtures of the polio virus vaccines with other immunizing agents and adjuvants in common use will be, and what long-range effects on epidemic patterns a reduction in opportunity for acquiring a natural immunity will have.

Reports have appeared that primary immunization with Salk vaccine may produce lifelong immunity.[26] If this is so, it contradicts experience with immunization against any other disease; boosters have been necessary for continued immunity. The argument that exposures to the polio viruses will maintain immunity through a natural booster effect may not be sound. As the polio viruses become less prevalent, the opportunity for exposure will diminish, as has happened with diphtheria. The argument that persons vaccinated against poliomyelitis will be protected from paralysis by rapid antibody recall before central nervous system invasion occurs can be verified only by prolonged field experience. One may not place reliance on a rapid antibody recall many years following a relatively weak primary antigenic stimulus.

We should not overlook the possibility that depriving persons of an opportunity to acquire and maintain a natural immunity may produce a susceptible population; serious epidemics might result. The only claim that can be supported concerning the protective value of Salk vaccine pertains to the months immediately following immunization. Until boosters are proved unnecessary, it would appear to be sound practice to administer them as is done with other immunization procedures.

Further reports have appeared that Salk vaccine is effective when combined with diphtheria, whooping cough and tetanus vaccines.[27] It is not easy to arrive at an adequate measure of vaccine effectiveness. The elaborate field trials of the Salk vaccine in 1954 and the field trials going on under the auspices of the British Medical Research Council to test the effectiveness of DPT combined antigen testify to this. Much painstaking study must be done before poliomyelitis vaccine can be added to DPT for routine immunization.

Efforts are being made to develop other polio virus vaccines. Historical review of immunizing agents indicates that it would be surprising if more effective agents and refinements did not appear. One such effort is to make a vaccine of living polio viruses which retain their ability to produce antibodies but are attenuated in that they are not pathogenic. Wenner[28] has reviewed the problems associated with such a living vaccine.

Adults as well as children need protection from poliomyelitis. Only 50 per cent of adults are immune to all three types of polio virus. It is reported that in temperate climates an increasing number of adults are afflicted with poliomyelitis, and the afflictions are apt to be more serious than in younger age groups.

Procedure—The recommended course of immunization consists of giving two doses of 1.0 ml. of Salk vaccine intramuscularly a month apart, and a third dose seven months later. Longer intervals between injections do not diminish their effectiveness.[25]

Suggested Immunization Schedule

The following schedule of immunization seems reasonable on the basis of our present knowledge.

Primary immunizations:

AGE	AGENT
2 months	0.5 ml. DPT (with adjuvant)
3 months	0.5 ml. DPT (with adjuvant)
4 months	0.5 ml. DPT (with adjuvant)
5 months	Smallpox vaccination
6 months	1.0 ml. Salk vaccine
7 months	1.0 ml. Salk vaccine
14 months	1.0 ml. Salk vaccine

Changes in sequence of injections, type of antigen, and intervals between injections may be indicated for local epidemiologic or individual reasons. Greater intervals between injections than those indicated are not disadvantageous except for the delay in completing immunization.

Boosters:

AGE	AGENT
18 months	0.5 ml. DPT (with adjuvant)
4 years	0.5 ml. DPT (with adjuvant); smallpox vaccination
7 years	0.25 ml. DT (with adjuvant)
10 years	Smallpox vaccination; Schick test; diphtheria toxoid sensitivity test; 0.25 ml. DT (with adjuvant) if Schick test is positive and toxoid sensitivity test is negative; otherwise 0.25 ml. T (with adjuvant)

The booster schedule listed for age 10 years should be repeated every three years, except for smallpox vaccination which is done every five or six years. Additional boosters with fluid toxoids, and revaccination against smallpox may be necessary due to risk of exposure.

As yet, data are not available to indicate how frequently boosters of Salk vaccine must be given, if at all. It would not be unreasonable to give booster injections of 1.0 ml. every three years until contradictory information becomes available.

Contraindications to Immunization

One should not immunize any child with a respiratory or any other acute infection until he recovers completely. One may immunize allergic children;[29] however, any dermatitis, including eczema, involving the patient or a close contact contraindicates vaccination against smallpox. Children with convulsive disorders should be immunized,[30] probably with fractional doses.

During a local outbreak of poliomyelitis one should defer elective DPT injections because of a slightly greater risk of the development of paralytic poliomyelitis involving the injected extremity.[31]

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Postgraduate Clinical NOTES

81. EUTHANASIA AND THE LAW

"You have heard a good deal of discussion during the evidence about the circumstances in which doctors might be justified in administering drugs which would shorten life. Cases of severe pain were suggested and also cases of helpless misery. The law knows of no special defence of this category. But that does not mean that a doctor who is aiding the sick and dying has to calculate in minutes or even hours, perhaps not in days or weeks, the effects on a patient's life of the medicines which he will administer.

"If the first purpose of medicine—the restoration of health—can no longer be achieved, there is still much for the doctor to do, and he is entitled to do all that is proper and necessary to relieve pain and suffering even if the measures he takes may incidentally shorten life. There are cases in hospital where a doctor prolongs or shortens life by hours or perhaps even longer. The doctor who decides to administer the drug or not is not thinking in terms of hours or months of life. He could not do the job if he were. If, for example, a doctor has done something or omitted to do something and death occurs, say on the eleventh or twelfth or on the Monday instead of the Tuesday, no one with common sense would say the doctor caused the death. They would say the cause of death was the injury or whatever it was that brought her to hospital. It remains a fact and remains the law that no doctor, nor any man, has the right to deliberately cut off life. I say it to you so there can be no mistake."

Summing-up by Mr. Justice Devlin in the case of Dr. John Bodkin Adams, found "not guilty" of the murder of Mrs. Morriee,
British Medical Journal, April 20, 1957, p. 954

Differential Diagnosis of Back Pain

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BACK pain is one of the most common complaints encountered in any doctor's practice. In this day of an expanding social welfare state, doctors are being called on more and more to substantiate claims for disability based on the complaint of backache. A great portion of the patients have claims for disability through the Workmen's Compensation Act in their individual states. Many of these complaints of backache are related to third party litigation. A further number will rapidly appear with the recent expansion of social security benefits under the Old-Age and Survivors' Insurance program.

Certainly, no one should or will deny the relationship between backache and injury. On the other hand, it is well to recapitulate from time to time the various conditions other than injury which may be productive of pain in the back. There is nothing new in this paper. All of the facts referred to are well recognized and have been for many years. Proper and complete evaluation of backache demands a very careful detailed history and general physical examination before the conclusion can be reached that injury, and injury alone, is responsible for the complaint.

Postural deformity is the most common cause of backache. A slouchy attitude, with increase in lumbar lordosis and a thoracic kyphosis, may be habitual or the end result of a juvenile osteochondritis that appeared during adolescence. The slouchy attitude can be corrected with proper postural training during school years. The lordosis and kyphosis can be minimized by early recognition and proper treatment during the active phase of the disease.

Certain occupational attitudes can be productive of backache, e.g., the individual who sits slouched over a desk at work 10 hours a day and makes no effort to compensate with exercise away from work. Bad seating is frequently forgotten or ignored. Resting in soft sagging beds after a hard day's work can and often does produce backache.

Shortness of one leg can produce a scoliosis and tilt of the pelvis, and many times creates pressure on the root of the opposite twelfth thoracic nerve to produce back pain. Usually, man can accommodate quite satisfactorily for shortening of one-half to three-fourths inch, but anything beyond this can lead to difficulty. Recognition of the problem by measurement of leg length is frequently forgotten. Many patients have had lengthy genitourinary in-

vestigations with a large investment in x-rays to alleviate the flank pain that could have been cured promptly by adjustment of the inequality of leg length with a heel lift.

Shortness and contracture of the musculature of the lower extremities and the fascial structures frequently fail to be recognized. People who work in an automobile or at a desk very often will develop contractures of the hamstring and calf muscles sufficiently severe to produce chronic backache of rather severe grade. One of the other very common causes of muscle and fascial contractures in the lower extremities is a protracted illness with prolonged recumbency. Stretching out these contracted fascial bands and muscles with exercise can be done.

Postural backache can develop because of a generalized muscular debility or with increasing age. The patient in the fourth or fifth decade of life who has allowed generalized muscle deterioration to occur has acquired heavy layers of fat across the abdomen, torso and thighs, which will produce chronic backache. Actual postural factors produce more backache than does injury.

Certain specific diseases of the spinal column produce backache. Many of these fall in the field of arthritis. One of the most pernicious is Marie-Strümpell disease. This characteristically appears in the male, occasionally in the female, and will usually manifest itself during the second or third decade of life. Any young person with backache should be presumed to have Marie-Strümpell disease until its presence has been disproved. One of the earliest manifestations is a restriction in the chest expansion. No young adult with backache should fail to have his chest expansion accurately recorded and checked at several intervals over a period of months. Usually, with a limited chest expansion and with some evidence of increase in the sedimentation rate of the erythrocytes, the disease entity can be assumed to be present long before roentgenologic changes become evident. Deformities can be minimized, if not completely avoided, with early recognition of the disease and properly directed treatment.

Rheumatoid arthritis can attack the spinal column alone, although it more commonly is associated with similar disease processes in the extremities, especially the hands. Certain specific infections, such as tuberculosis or osteomyelitis, must be kept in mind.

There are certain disease entities related to generalized metabolism that are productive of backache. I am referring particularly to the type of osteoporosis of the spinal column seen in the aged (so-called senile osteoporosis) and that type of osteoporosis which is due to disturbance in function of the parathyroid glands. Many of the patients have chronic backache of many years' duration, and many of them have spontaneous collapse due to fracture. The entity is easily recognized in its end stages. On the other hand, its presence will not be recognized unless it is suspected in its early stage. I recall a physician's wife who was treated as an arthritic for some years before it was finally recognized that her basic difficulty was a congenital dysfunction of ovarian tissue which produced a premature menopausal osteoporosis.

Some diseases of the blood, for example, myeloid and lymphoid leukemia, may produce erosion of a vertebral body and cause disabling pain. Aneurysm of the thoracic or abdominal aorta may manifest itself by backache. Certain malignant diseases frequently attack the spinal column. Multiple myeloma, metastatic carcinoma and Hodgkin's disease are three of the most common. Ewing's tumor may attack the spinal column. Occasionally, an osteoid osteoma will do the same. Backache is probably the most common initial symptom associated with malignant retroperitoneal fibrosarcoma.

Certain diseases outside of the spinal column must be kept constantly in mind. Any acute infection, local or general, can be productive of backache. In some diseases of the abdominal viscera, the initial symptom frequently is backache. Peptic ulcer and retrocecal appendix are two. Carcinoma of the stomach, duodenum or tail of the pancreas is a frequent offender.

In the initial stage of certain disease entities within the pelvis, such as benign and malignant tumors of the ovaries or uterus, the

only symptom may be back pain. Widespread pelvic adhesions due to pelvic inflammatory disease were probably more common in years gone by; since the advent of antibiotics, they are less frequently seen, but still occur. Positional defects of the uterus, such as a retroversion, must be recognized. The presence of stones in the kidney, ureter or bladder may frequently be missed without careful investigation. Although the relation of prostatic disease to backache received a great amount of unwarranted stress a few years ago, it can cause disabling back pain that can only be eradicated by specific measures directed toward this organ.

Certain specific infections which appear in the retroperitoneal space, such as abscesses of the kidney, perinephritic abscess, retroperitoneal abscess, abscesses in the substance of the iliacus muscle, will be unrecognized unless measures are taken to search for them specifically.

Many congenital malformations of the spinal column are thought to be the cause of backache, and they frequently receive undue attention in the differential diagnosis of the cause of this condition. Some of the common congenital malformations of the spinal column are as follows: (1) hemivertebra; (2) extra lumbar vertebra; (3) extra sacral vertebra; (4) abnormal or irregular lumbar facets; (5) sacralization of the last lumbar and first sacral vertebrae; (6) scoliosis, idiopathic or acquired, paralytic or nonparalytic; (7) spondylolysis, and (8) spondylolisthesis. These malformations rarely are the only cause of serious backache. In some cases in which roentgenologic examination reveals serious deformity of the spinal column, backache may occur with advancing age, and osteoarthritic changes may occur in the later decades of life. One of the difficult problems in cases of backache is spondylolisthesis. Many persons who have severe spondylolisthesis are able to do heavy manual labor without having any appreciable backache at any time during life.

Occlusive disease of the abdominal aorta, the common iliac artery, or right or left femoral artery may produce a symptom complex which can easily be confused with primary disease of the spinal column. Occlusive disease of one of the renal arteries occasionally will produce the same symptom complex. In the differential diagnosis of the causes of backache, it is absolutely necessary to determine whether or not a major artery is occluded. This is especially true in cases in which the patients are in the fifth or sixth decade of life. In many cases, an unnecessary spinal operation has been performed because of the failure to eliminate the possible presence of occlusion of a major artery.

The effects of injury of the spinal column may be as follows: (1) local contusion of the musculature; (2) strain or sprain of the muscles or ligaments supporting the spinal column; (3) partial or complete dislocation of the intervertebral facets; (4) fracture, and (5) injury of the intervertebral disks. Most fractures and dislocations can be disclosed by adequate roentgenologic examination. The diagnosis of injury of the intervertebral disks may require careful and repeated neurologic examination over a protracted period.

An emotionally unstable person, a typical psychoneurotic, unfortunately too often will complain of backache as his chief symptom.

Last and least important of all from a diagnostic viewpoint is the group of people who are definitely malingerers or victims of so-called compensationitis. Unfortunately, our expanding social welfare theorists are creating more and more occasion for this last disease category, but the diagnosis should never be made except as a last resort when all other possibilities have been carefully excluded.

Without any attempt, therefore, to present an erudite discourse on backache, it would appear that the prime requisite of the attending physician examining the patient with the presenting complaint of backache is that he exercise every care and diligence at his command to obtain a very careful and detailed history covering all medical aspects of the individual, that he complete and record a detailed physical examination, and co-ordinate his findings with proper laboratory and x-ray studies. It takes the services of a good doctor of medicine, not a specialist, to evaluate the complaint of chronic backache properly.

Colonic Polyps: Report of Three Cases

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POLYPS of the colon should be removed because they are potentially precancerous. Moreover, a patient who has had a polyp should be re-examined every year, inasmuch as the chances of a new polyp developing are 28 per cent[1] and the risk of carcinoma is high. Figures 1 to 3 illustrate how a polyp may develop into a carcinoma and may extend. The following cases are reported to demonstrate the importance of annual examination.

CHARLES W. MAYO

MARTIN Y. LABERGE

Case Reports

Case 1—A white woman, 58 years of age, first visited the Mayo Clinic in February 1942, complaining of having had blood in the stools and increasing constipation since hemorrhoidectomy, performed six months earlier. On proctoscopic examination, a large, obstructing, annular growth was found 12 cm. from the dentate margin. On biopsy the diagnosis was adenocarcinoma, grade 1 (Broders' classification). Extraperitoneal resection and colostomy were performed, the temporary colonic stoma being drawn close about a catheter. The growth measured 6 by 5 by 2 cm. The peritoneum and one regional lymph node were involved (a "C case" according to the classification by Duke).

In 1957, when the woman was seen at the clinic again, at the age of 72 years, a polypoid lesion, above the old anastomosis, extended upward for 5 cm. On biopsy the diagnosis was sessile adenomatous polyp. The

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FIGURE 1. Adenocarcinoma, grade 1, in an adenoma. The stalk was not involved. Local excision of the polyp is sufficient.

growth was removed transabdominally on January 7, 1957; this was an "A case," according to Duke's classification.

Case 2—In 1954, a white man, 71 years of age, came to the Mayo Clinic because of pain in the thorax. At that time he also complained of "burning piles" and chronic constipation. The proctoscopist saw a polypoid, sessile lesion situated 11 cm. from the dentate margin, to the left of the median line. Biopsy and fulguration, after roentgenologic examination of the colon, were advised. However, the man had to go home immediately but expected to return in a few days.

Unfortunately, he did not return until January 1957, when he was 74 years of age. His chief complaint at that time was of rectal bleeding of two months' duration. The polyp, which formerly had appeared to be benign, had become a fixed, ulcerated, nonobstructing lesion, 2.5 cm. in diameter. It was an adenocarcinoma, grade 2 (Broders' classification) for which low anterior resection, with

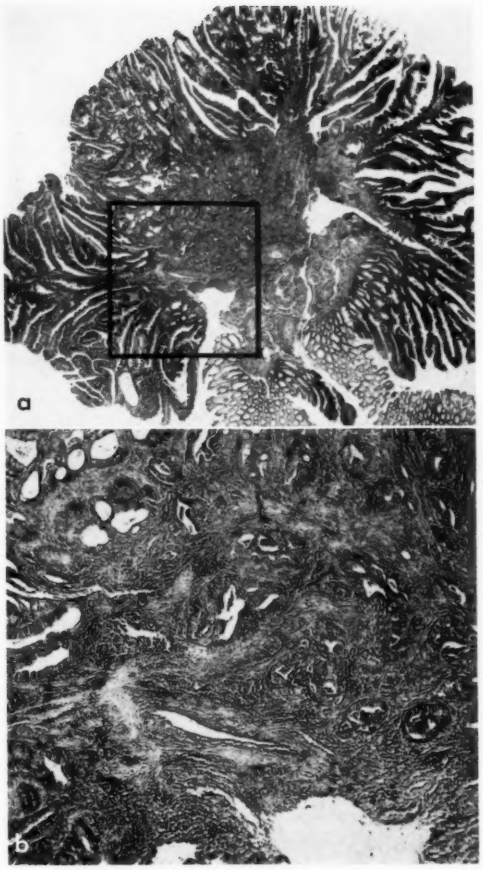

FIGURE 2a. Adenocarcinoma, grade 1, in an adenoma with involvement of the stalk as shown in b. Segmental resection of the colon is necessary.

FIGURE 3. Small polyp containing an adenocarcinoma, grade 1, with involvement of the stalk and of a lymph node.

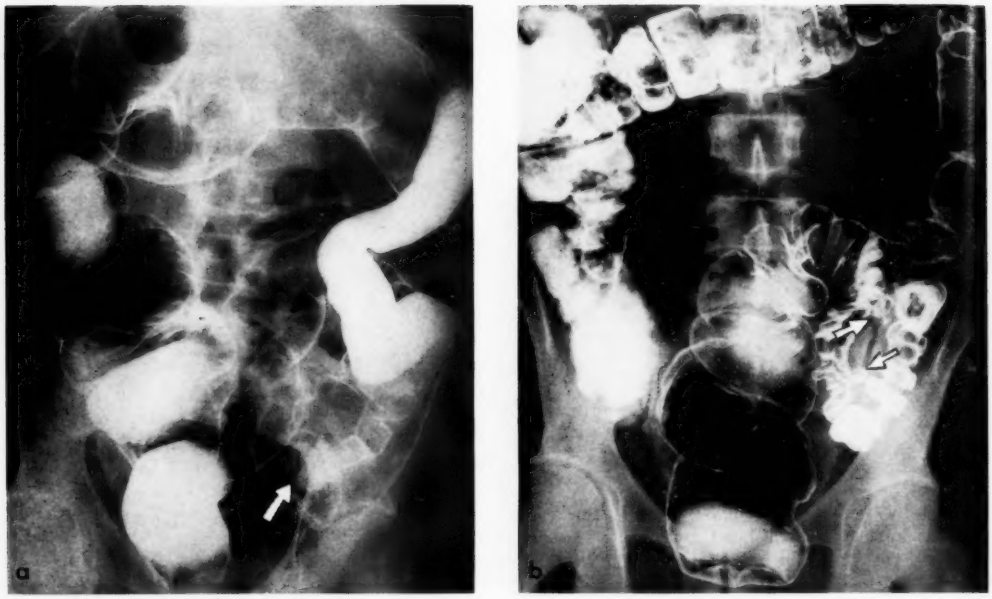

FIGURE 4. Case 3. a. The polyp, evidence of the presence of which in the upper part of the sigmoid had been found in 1946, appeared to be of unchanged diameter in 1950. b. In 1957, evidence of malignancy was found in the same region.

end to end anastomosis, was performed. The growth extended through the wall of the bowel and into the perirectal fat. All resected nodes were negative to examination but one vein was involved.

Case 3—In 1946, a Negro, 45 years of age, was examined at the Mayo Clinic and a polyp was found on the right rectal wall, 14 cm. from the dentate margin. The polyp was fulgurated and roentgenologic examination gave evidence of the presence of another polyp, about 2.5 cm. in diameter, near the junction of the sigmoid and descending colon. This polyp was too high in the colon to allow of its fulguration by the proctologist. Although the nature of the lesion indicated abdominal operation, it was not advised because of the patient's general condition; some aortic stenosis, with left ventricular failure and hypertension, was present. The patient was advised to undergo annual roentgenologic examination of the colon.

He returned in 1950, at which time the radiologist reported that the size of the lesion had not changed (figure 4a). The patient returned again in 1957, when he was 56 years of age; his only complaint referable to the gastrointestinal tract was of increased constipation. A broad-based, sessile lesion, 5 cm. in its greatest diameter, was found at the site of the polypoid lesion in the upper portion of the sigmoid (figure 4b). The descending colon, sigmoid and rectosigmoid were resected. The lesion was an annular, ulcerative adenocarcinoma, grade 2 (Broders' classification; figure 5), which involved the muscularis. Involved lymph nodes were not found.

Comment

The incidence of polyps found at postmortem examination varies with the ages of patients. Polyps are found in the colons of only 2.5 per cent of persons who come to necropsy at less than 30 years of age, but polyps are present in the colons of 14.2 per cent of those who are more than 50 years of age. The situation of polyps in the colon is approximately the same as is that of carcinomas of the colon.

FIGURE 5. Case 3. The lesion was an adenocarcinoma, grade 2, with involvement of the muscularis.

In one month, 176 of 1,525 patients referred for proctoscopic examination at the Mayo Clinic were found to have rectal polyps.[2] Most of the polyps were asymptomatic. They were treated by fulguration alone or, if the lesion was large, fulguration was preceded by biopsy. The finding of a polyp by sigmoidoscopy should be followed by roentgenologic examination of the colon to determine whether there are lesions higher in the bowel. For lesions situated above the reach of the sigmoidoscope, roentgenologic examination, by the double contrast technic, is the only available means of diagnosis. If a single polyp is found, it is excised. At the same time, digital search of the lumen, proximal and distal to the incision, is made for other polyps that might not have been found on roentgenologic examination. A sigmoidoscope also can be introduced for this purpose.

If there is more than one polyp in a part of the bowel, segmental resection is performed. If polyps are scattered about the colon, a more radical surgical procedure is indicated, such as hemicolectomy, or even subtotal colectomy, with removal of that portion of colon most susceptible to the development of polyps.

Although most colonic polyps are benign, some removed polyps are found to have undergone malignant change. An adenomatous polyp may remain benign, or it may become malignant after having remained benign for 10 to 20 years. The first malignant transformation usually is seen in the tip of the polyp; later, the stalk becomes infiltrated. If ulceration is present, the entire polyp may slough off and the cellular invasion may continue into the wall of the bowel.

The early microscopic changes seen in the tip of a polyp are confined to the nuclei of the cells. These changes are (1) hyperchromatism, (2) variation in size and shape, (3) atypical mitotic figures, and (4) loss of normal alignment with their neighbors.

Because colonic polyps are common precancerous lesions; because the majority of colonic carcinomas probably develop in polyps, and because patients who have, or have had, colonic polyps are vulnerable to the development of new polyps and therefore of carcinoma, it is of supreme importance for such patients to undergo re-examination at least once a year.

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Emergency Treatment of Severe Asthma

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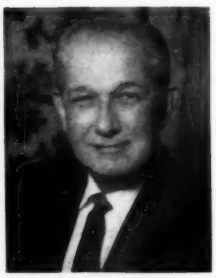

STANLEY F. HAMPTON

ALTHOUGH the morbidity of asthma has been reduced since the advent of ACTH (corticotropin) and the adrenal corticosteroids, the mortality rate still is significant. The U. S. vital statistics show that the death rate increased from 1.8 per 100,000 in 1948 to 4.5 in 1951 and 1952.[1] The death rate has decreased to 3.8 per 100,000 in 1954 and to 3.6 in 1955.[2]

There is no universal classification of the types of asthma. For the sake of clarity, I shall use a classification similar to that suggested by Rackemann.[3] Extrinsic asthma is due to allergens from without the body. These include pollens, air-borne molds, animal danders and other inhalants, foods, antibiotics and foreign sera. Intrinsic asthma is due to factors within the body. The principal etiologic factors appear to be infection and/or perhaps hypersensitivity to pathogens or even nonpathogenic bacteria of the respiratory tract. The fact that sputum cultures of patients with intrinsic asthma with or without fever or leukocytosis rarely reveal organisms other than those normally present in the respiratory tract suggests that hypersensitivity to nonpathogenic bacteria may be a mechanism in producing asthma.

In 1917, Walker[4] reported that a complement fixation test performed with an antigen prepared with *Staphylococcus pyogenes aureus* was positive in three of six cases of intrinsic asthma. In one of the three cases, a subsequent reaction was found to be negative after the patient had been desensitized by administration of four doses of the antigen. Swineford[5] produced anaphylactic shock in sensitized guinea pigs by aerosolization with *Pneumococcus* polysaccharide, and Swineford

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and Holman[6] showed that the sera of several patients contained skin-sensitizing antibodies for the polysaccharides and the nucleoproteins of common respiratory bacteria. Beiser, Dworetzky, Smart and Baldwin,[7] by using the agar precipitin method of Ouchterlony,[8] showed that human serum contained antibodies for material derived from *Staph. aureus*.

Numerous other reports tend to support the hypothesis that hypersensitivity to antigens of respiratory bacteria may be the cause of intrinsic asthma. However, in an appreciable number of cases of severe asthma, the patients do not have any demonstrable evidence of infection when they consult a physician, and the cause of the asthma is obscure. It is within the realm of possibility that autosensitivity may play an etiologic role in some cases of intrinsic asthma in the same manner as it has done in cases of experimental glomerulonephritis, rheumatic fever, certain blood dyscrasias and diseases of the central nervous system reviewed by Cavelti.[9]

Although extrinsic asthma may be severe, it usually responds readily to the administration of epinephrine (ADRENALIN®) by the subcutaneous route or by nebulization or to the intravenous or rectal administration of theophylline preparations such as aminophylline even if it is not relieved by the oral or rectal administration of other drugs. Extrinsic asthma rarely develops into status asthmaticus. If asthma fails to respond to ordinary antiasthmatic drugs, it should be considered intrinsic and more drastic therapeutic measures should be employed.

Treatment of Bronchospasm

The bronchospasm of asthma usually responds favorably to subcutaneous injection of a 1:1000 solution of epinephrine in doses of 0.25 to 0.5 cc. for adults, to hand nebulization with a 1:100 solution of epinephrine, a 1:100 to 1:200 solution of isopropylepinephrine or isopropylarterenol hydrochloride (ALUDRINE® hydrochloride; ISUPREL® hydrochloride) or a similar solution of isopropylarterenol sulfate (NORISODRINE® sulfate), to sublingual administration of preparations of isopropylarterenol, and to oral administration of ephedrine and ephedrinelike drugs. Theophylline compounds, such as aminophylline, are most effective when administered by intravenous infusion. When these compounds are administered in this manner, 250 mg. in 10 cc. of solution is infused in 5 or 10 minutes or as much as 1 gm. in 1000 cc. of solution is infused in three hours. Sodium iodide and ACTH may be added to the solution.

Although preparations of theophylline are relatively ineffective when administered orally, they are of value when administered rectally as solutions, aqueous suspensions or as suppositories. Recently, theophylline compounds such as CARDALIN® and ELIXOPHYLLIN®, which can be taken orally, have received attention. Dihydroxypropyl theophylline,* now under investigation, has been quite effective as a bronchodilator in selected cases.

Treatment of Edema of the Bronchial Mucosa

The therapeutic agents recommended for the treatment of bronchospasm tend to reduce the edema of the bronchial mucosa. This condition, however, responds best to the administration of ACTH or corticosteroids.[10-12] These therapeutic agents, by reducing tissue inflammation, may well reduce the excessive production of sputum, which is the most important phase of severe asthma.

ACTH—This may be administered by three methods: (1) by continuous intravenous infusion, (2) by intramuscular injection, and (3) by both intravenous and intramuscular routes.

Continuous intravenous infusion for from 24 hours to several days is the method of choice when practical. When ACTH is administered in this manner, the daily dose is 30 units, and each 10 units is administered in 1000 cc. of a 5 per cent aqueous solution of dextrose. In most cases, the infusion can be accomplished without open exposure of a vein, although it is advisable to permit the solution to flow freely through the tubing and needle for a few seconds or minutes every two to four hours to avoid clotting in the needle. Disad-

*Supplied by the Schering Corporation.

TABLE 1

EFFECT OF ACTH ON THE TOTAL EOSINOPHIL COUNT

CASE	METHOD OF ADMINISTRATION	DAILY DOSE	TOTAL EOSINOPHIL COUNT, PER CUBIC MILLIMETER*				
			Before administration	*24 hr. later*	*48 hr. later*	*12 hr. later*	*96 hr. later*
B. J.	Intramuscular (ACTH gel)	40 units	935	211	231	319	253
C. B.	Intramuscular (ACTH gel)	40 units	385	211	231	0	0
F. N.	Intravenous and intramuscular	10 units intravenously; 10 units intramuscularly	242	155	122	111	78
H. C.	Intravenous and intramuscular	10 units intravenously; 10 units intramuscularly	198	125	56	62	0
M. F.	Continuous intravenous infusion	20 units†	642	0	0	22	0
H. E.	Continuous intravenous infusion	30 units	2175	1250	0	6	0

*The eosinophil counts were made while the patients were fasting.

†Each 10 units was administered in 1000 cc. of a 5 per cent aqueous solution of dextrose.

vantages of this method of administration are anxiety of the patient, extravasation of fluid, and, at times, plugging of the needle.

When ACTH is administered intramuscularly in the form of ACTH gel, 40 to 80 units is administered once a day at one time or in divided doses at intervals of 12 hours. There has been interest in corticotropin zinc hydroxide, an aqueous preparation which has a prolonged action.[13]

ACTH may be administered both intravenously and intramuscularly. When it is administered by both of these methods, 10 units is administered intravenously in 1000 cc. of a 5 per cent aqueous solution of dextrose in a period of eight hours, and 20 to 40 units is administered intramuscularly in the form of ACTH gel midway between the intravenous injections, usually about midnight. This combined method of administration is a substitute for continuous intravenous infusion.

Observations of the clinical improvement and the effect on the total eosinophil count (table 1) and the urinary excretion of 17-ketosteroids (table 2) indicate that continuous intravenous infusion is the preferable method of administration when practical. If patients are treated in the hospital, it is recommended that ACTH be administered by continuous intravenous infusion until the period of emergency is over and that ACTH gel be administered subsequently by the intramuscular method. If patients are not hospitalized, ACTH gel should be administered intramuscularly.

Intensive administration of ACTH should not be discontinued abruptly. The dose should be reduced gradually over a period of several days unless the intensive administration is to be followed by a course of corticosteroids.

Corticosteroids—Prednisone (METICORTEN®, DELTRA®) and prednisolone (METICORTELONE®, DELTA CORTEF®, HYDELTRA®, STERANE®) which are new corticosteroids, have proved to be more effective than their precursors cortisone and hydrocortisone in the treatment of asthma. In a series of more than 600 cases of allergic disease, chiefly asthma, some of which have been reported previously,[12] it was observed that Meticorten and Meticortelone* were effective therapeutic agents and that their effectiveness approached that of ACTH gel. Their principal advantages

*The Meticorten and Meticortelone used in these cases was supplied by the Schering Corporation.

TABLE 2

EFFECT OF ACTH ON URINARY EXCRETION OF 17-KETOSTEROIDS

CASE	METHOD OF ADMINISTRATION	DAILY DOSE	MG. OF 17-KETOSTEROIDS EXCRETED IN 24 HR.*		
			Before administration	*24 hr. later*	*96 hr. later*
L. I.	Intramuscular (ACTH gel)	40 units	8.7	11.6	18.9
B. C.	Intramuscular (ACTH gel)	40 units	4.7	5.9	20.4
F. N.	Intravenous and intramuscular	10 units intravenously; 10 units intramuscularly	13.4	24.7	33.7
S. W.	Intravenous and intramuscular	10 units intravenously; 10 units intramuscularly	9.4	13.9	23.4
H. R.	Continuous intravenous infusion	20 units†	18.6	44.3	66.6

*The excretion of 17-ketosteroids was determined in the Metabolism Laboratory of the Washington University School of Medicine under the direction of Dr. William H. Daughaday.

†Each 10 units was administered in 1000 cc. of a 5 per cent aqueous solution of dextrose.

are as follows: (1) They are effective when administered orally, and (2) they do not cause retention of sodium and water when administered in a daily dose as large as 20 mg., which usually is effective in cases of moderately severe asthma. There recently has been interest in the use of a new corticosteroid, TRIAMCINOLONE® (9 alpha-hydroxyl-delta-1-hydrocortisone diacetate) in the treatment of allergic disease.[14] Further studies will be needed to determine the clinical effectiveness and the side effects of this compound.

Although peptic ulcer and pulmonary tuberculosis have been considered contraindications to the administration of ACTH and adrenal steroids,[15,16] recent evidence indicates that these agents may be of value in treating tuberculosis when they are combined with specific antimicrobic therapy.[6] The administration of a full therapeutic dose of a corticosteroid should not be discontinued abruptly; instead, the daily dose should be reduced gradually over a period of several days or weeks, depending on the length of time that the drug has been administered.

If severe asthma develops in a case in which a corticosteroid has been administered for several weeks or longer, if trauma occurs, or if a major operation becomes necessary, the administration of the corticosteroid should not be discontinued, but the dose should be increased during the period of stress, regardless of whether or not the administration of ACTH is started.

Removal of Tenacious Sputum From the Bronchial Tree

If death occurs in cases of asthma, it usually is the result of anoxia due to tenacious mucus occluding the bronchioles.[17] Figure 1 is a photograph of the lung of a patient who died of asthma. The entire bronchial tree of this patient was plugged with tenacious mucus.

The agents used in the treatment of bronchospasm and edema of the bronchial mucosa may loosen the mucus plugs and thus facilitate expectoration. The use of specific measures for this purpose frequently is lifesaving. It is most important that the patient with asthma cough and produce sputum.

Potassium iodide, sodium iodide, calcium iodide, hydriodic acid, lobelia, ammonium chloride, glycyrrhiza, glycerin, terpin hydrate, ipecac, white pine and wild cherry are useful expectorants, but potassium iodide and sodium iodide are the expectorants of choice in cases of severe asthma. Potassium iodide is administered orally in daily doses of 3 to 6 gm., and sodium iodide is administered intravenously in doses of 1 to 2 gm. in 500 to 1000 cc. of solution. It may be combined with solutions of theophylline and ACTH. It should not be administered intravenously until the oral administration of a test dose has demonstrated

FIGURE 1. Tenacious mucus extending from a bronchus to bronchioles in lung of patient who died of asthma.

From Hampton, S. F.: Status asthmaticus. Missouri Med. 54:229 (March) 1957.

that the patient is not hypersensitive to the iodides. Skin tests with iodides, as with drugs in general, usually are not reliable.

Aerosols of bronchodilators and sputum solvents, particularly when used with intermittent positive pressure breathing,* recently have been of interest and appear to be of value in promoting bronchial drainage. Numerous reports, including those by Barach, Bickerman and Beck,[18] Segal and Dulfano,[19] Wu, Miller, Cade and Richburg,[20] and others, support the use of bronchodilators such as epinephrine and isopropylarterenol and of detergents such as ALEVAIRE® and TERGEMIST® in the nebulizer of the apparatus used for intermittent positive pressure breathing. Some authors[21,22] have felt that these agents are just as effective when administered alone as they are when used with intermittent positive pressure breathing. It has been my experience that the use of bronchodilators and sputum solvents in the nebulizer of the apparatus used for intermittent positive pressure breathing has been a most valuable aid in several cases of severe asthma. It was a factor in preventing death in several cases of severe asthma and in cases of pulmonary emphysema and cor pulmonale. A suggested regimen is the use of 0.5 cc. of a 1:200 solution of isopropylarterenol hydrochloride or sulfate in 5 cc. of Alevaire in the nebulizer of the apparatus. Tergemist and a new preparation, ANTIFOAM® solution 5507X,† also may be used.

Barach, Beck and Smith[23] have advocated the use of an apparatus, known as the COF-FLATOR®‡ or EXSUFFLATOR®,§ by means of which positive pressure breathing is followed by sudden negative pressure which induces coughing. Although such a therapeutic approach seems sound theoretically, my impression is that the results have not been encouraging, but my experience with the procedure has been limited.

Aerosols of proteolytic enzymes, including TRYPTAR®[24] (crystalline trypsin) and pancreatic desoxyribonuclease[25] (pancreatic dornase) have been used as sputum solvents, but fur-

*Apparatus for intermittent positive pressure breathing is manufactured by V. Ray Bennett and Associates, Inc., and by the J. H. Emerson Company.

†The Antifoam solution was supplied by the Winthrop Laboratories, Inc.

‡The Cof-flator is manufactured by the Oxygen Equipment Manufacturing Corporation.

§The Exsufflator is manufactured by the Eliot Medical Plastics Company.

ther study is needed before the value of these enzymes can be evaluated. I have found Tryptar to be of value in certain cases. Since it may irritate the mucous membrane of the respiratory tract, it should be administered with caution. Doses of 50,000 to 125,000 units in 3 to 6 cc. of a diluent should be administered every six to eight hours for a limited time.

In cases in which the patients are moribund, aspiration with a bronchoscope or an endotracheal tube may be indicated, particularly after aerosols have been administered with intermittent positive pressure breathing.

Relief of Anoxia and Carbon Dioxide Retention

Comroe, Bahnson and Coates[26] first demonstrated that oxygen therapy actually may increase the retention of carbon dioxide in cases of asthma. In cases in which oxygen is administered, particularly by mask but also by a tent or nasal tube, the patients should be observed closely for increased narcosis, manifested by drowsiness or an increase in the carbon dioxide-combining power of the plasma, or both. The use of intermittent positive pressure breathing usually permits the administration of oxygen without the risk of increasing carbon dioxide narcosis.

Motley, Lang and Gordon[27] have reported that intermittent positive pressure breathing actually increases minute ventilation and facilitates the "blowing off" of carbon dioxide. Smart, Davenport and Pearson[28] found that administration of oxygen with the apparatus used for intermittent positive pressure breathing not only increased the arterial saturation over that produced by conventional administration of oxygen, but that it was a safer method for the administration of oxygen.

The use of DIAMOX®, a carbonic anhydrase inhibitor, does reduce the carbon dioxide-combining power of the plasma by reducing the plasma bicarbonate and the carbon dioxide in the arterial blood in some cases,[29] but it may lower the actual pH of the blood sufficiently to increase acidosis. A drug of this type, therefore, must be used with caution. I have found that the daily administration of 250 to 500 mg. of Diamox has been of clinical value in selected cases, particularly in those in which mild heart-failure is due to cor pulmonale.

The carbon dioxide-combining power of the plasma and apparently the carbon dioxide tension of the blood and alveoli can be reduced by the aid of the Drinker respirator. It is difficult for the patient to synchronize his respirations with the movements of the respirator, however, and the technical difficulties may preclude the use of this apparatus except in cases in which the patients are unconscious or semiconscious.

Elimination of Infection

When evidence of infection of the respiratory tract is present in cases of severe asthma, appropriate antibiotic or sulfonamide therapy is indicated. Although evidence of infection frequently is not demonstrable, it is reasonable to assume that an infectious process is present in cases of severe asthma in which extrinsic etiologic factors are not apparent. In such cases, administration of broad-spectrum antibiotics is justified even if fever, leukocytosis and other obvious signs of infection are not present. Furthermore, the use of such antibiotics as a precaution against "masked infection" is warranted during ACTH or corticosteroid therapy. Because of the high incidence of hypersensitivity to penicillin, the use of this antibiotic is not recommended unless it is specifically indicated by bacteriologic studies.

Alleviation of Anxiety

Sedation is an important phase of the treatment of severe asthma. The sedatives that are used most commonly probably are chloral hydrate and paraldehyde. These drugs may be administered orally or rectally. Fifteen to 20 cc. of ether in equal parts of olive oil may be administered rectally. Barbiturates and DEMEROL® hydrochloride should be used with caution, and morphine, because of its depressing effect on the respiratory center and its constricting action on the bronchi, should be avoided. Perhaps the tranquilizing drugs such as MILTOWN®, EQUANIL®, THORAZINE®, VALMID®, DORIDEN®, ATARAX® hydrochloride, ULTRAN®, SUAVITIL® and TRILAFON® will prove to be useful in alleviating anxiety.

Treatment of Congestive Heart-failure

Right-sided heart-failure of cor pulmonale may develop secondary to emphysema or severe asthma. A detailed discussion of the treatment of heart-failure does not come within the scope of this paper. It should be emphasized, however, that improvement in pulmonary ventilation by the various means previously discussed is as important in the treatment of heart-failure of cor pulmonale associated with asthma as is the treatment of heart-failure per se with digitalis preparations, diuretics and salt restriction.

Removal of Extrinsic Factors

Although severe asthma requiring emergency treatment usually is of the intrinsic type, a search should be made for extrinsic allergenic factors, and appropriate management should be instituted if such factors are found.

Summary

Severe asthma should be considered intrinsic until proved otherwise. The etiologic role of infection or hypersensitivity to bacteria should be considered. Treatment of severe asthma should include relief of bronchospasm and edema of the bronchial mucosa, removal of tenacious sputum from the bronchial tree, relief of anoxia and carbon dioxide retention, elimination of infection of the respiratory tract, and alleviation of the anxiety of the patient. Epinephrine and preparations of isopropylarterenol and theophylline are effective in the treatment of bronchospasm. ACTH and the new corticosteroids prednisone and prednisolone are of value in the treatment of bronchial edema. The use of aerosols of bronchodilators, detergents and possibly proteolytic enzymes with intermittent positive pressure breathing is a new and efficient method of treating severe asthma.

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Management of Hemolytic Disease of the Newborn

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JAUNDICE in the first day of life is abnormal. When it occurs it has grave significance because, unlike the mature brain, the newborn baby's brain may be permanently damaged during jaundice. The consequence of hyperbilirubinemia at this early age may be neonatal death or the crippling encephalopathy which is called kernicterus. It is equally true that exchange transfusion properly timed and repeated, if necessary, maintains the concentration of serum bilirubin at a low level and prevents this type of brain injury. Therefore, it becomes mandatory that early neonatal jaundice be recognized at its inception in order that the bilirubin in the serum may be kept within safe limits. A value of 20 mg. of indirect-reacting bilirubin per 100 ml. of serum has been accepted quite widely as the limit above which one is not always safe. In premature infants, kernicterus may occasionally result from bilirubin levels below this limit.

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Besides the dangers of brain injury, the hemolytic anemia may be serious very early, and rapidly developing severe anemia may cause anoxia or myocardial failure or both, and endanger the patient's life very soon after birth. This anemic group requires prompt application of exchange transfusion to save them.

Because of the emergency situation which jaundice appearing in the first day of life creates, prenatal anticipation of its occurrence, when possible, is the best insurance of the

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TABLE 1

SCHEME OF THE EIGHT RH BLOOD TYPES

CLINICALLY RH-POSITIVE PERSONS			CLINICALLY RH-NEGATIVE PERSONS		
Wiener	*Fisher*	*Per Cent*	*Wiener*	*Fisher*	*Per Cent*
Rh O	Dce	2.0	rh′	dCe	1.0
Rh O′	DCe	54.0	rh″	dcE	0.5
Rh O″	DcE	15.0	rh′ rh″	dCE	0.01
Rh O′ Rh O″	DCE	14.5	rh	dce	13.0
		85.5*			14.5*

*The percentage figures refer to the relative incidence in the white population.

timely use of exchange transfusion. Iso-immunization is the most common cause of first-day jaundice. The most common form of iso-immunization which results in the serious type of hemolytic disease requiring exchange transfusion is due to the Rh factor. Fortunately, hemolytic disease of the newborn due to Rh iso-immunization lends itself well to prepartum anticipation.

The anticipation of early neonatal jaundice due to hemolytic disease of the newborn depends on an accurate history and proper studies of the mother to detect the presence and degree of iso-immunization. Testing of all pregnant women for the Rh factor should be done routinely.

Rh iso-immunization accounts for the great majority of instances of hemolytic disease of the newborn which require treatment, and in more than 90 per cent of the cases the disease is caused by immunization to one antigen, the Rh_o or D antigen. Rh_o and D refer to the same antigen as named by Wiener, and Fisher and Race, respectively. Unfortunately, there has not yet been world-wide acceptance of any one nomenclature for the Rh-Hr system of blood antigens. There are three major Rh and three major Hr antigens. They were named by Wiener, the discoverer, Rh_o, rh′, rh″, Hr_o, hr′ and hr″. Fisher and Race, Englishmen, subsequently named the same antigens D, C, E, d, c, and e. Both classifications have come into wide usage, and divide the six antigens into pairs: Rh_o and Hr_o (D and d), rh′ and hr′ (C and c), and rh″ and hr″ (E and e). The cells from a given individual contain one antigen from each pair from each parent. Therefore, his cells may contain all six of the antigens if he takes a different one from each pair from each parent, or as few as three if he takes the same one from each pair from each parent. What he takes from each parent is determined by what the parent cells contain.

The Rh antibodies are named according to their specificity as anti-Rh_o (anti-D), anti-Hr_o (anti-d), etc. Antibodies are also designated sometimes according to the percentage of the white population which they detect; for example, the anti-D serum reacts positively with the red cells of 85 per cent of the white population and is sometimes spoken of as the 85 per cent serum. Because the D (or Rh_o) antigen is responsible for such a great preponderance of all cases of hemolytic disease of the newborn caused by Rh or Hr iso-immunization, the clinical classification of the Rh phenotypes places all of those bloods which do not contain the Rh_o (or D) antigen in the clinically Rh-negative group (table 1).

The 85 per cent serum (anti-Rh_o or anti-D) determines positivity or negativity, because any person who lacks this antigen in his or her blood is just as easily immunized by it as an individual who lacks all of the Rh antigens. For these reasons, Rh testing is done with serum which has anti-D (Rh_o) (85 per cent) specificity alone. This serum detects the D antigen only, and for clinical purposes in obstetrics this is most important. When anti-CD (87 per cent) serum is used for testing, it falsely types the patient whose red cells contain C in the absence of D as Rh positive.

Such a patient is not Rh positive from a clinical standpoint, because she is just as promptly immunized to D as any patient whose red cells lack all of the Rh antigens. This false typing as Rh positive may lead to serious consequences if the problem of hemolytic disease is dismissed because of the results of the Rh testing. The use of anti-CDE serum has the same objection.

Anti-D (85 per cent) serum alone should be used in testing the husbands of all Rh-negative pregnant women. Should they prove to be Rh negative with the anti-D serum, they should then be tested for the Du variant of the D factor. As an aid in anticipating hemolytic jaundice in future newborn children of an Rh-negative woman and an Rh-positive husband, the husband's most probable zygosity may be determined. It may be impossible to determine his true zygosity directly by use of serum because of the unavailability of anti-d serum. After typing with the five available sera, the probable genotype is arrived at on the basis of the calculated frequency of Dd genes in the population. Charts showing this calculated frequency are available from manufacturers of typing sera as well as in published material. Typing of the husband's parents, when available, may make the determination of zygosity conclusive rather than probable. If he is a homozygous D-positive person and his wife is Rh negative, all of their children will be Rh positive and, if and when the mother becomes immunized, all subsequently born babies may be affected by hemolytic disease. If he is heterozygous positive, only one-half of the children may be affected since one-half of them will be Rh negative.

During the first pregnancy, it is safe to advise an Rh-negative wife and an Rh-positive husband to forget their Rh factor problem only if it is certain that the mother has had no transfusions or intramuscular injections of Rh-positive blood. Rh-positive blood either as a transfusion or intramuscular injection into an Rh-negative recipient may be sensitizing. If an Rh-negative mother has had transfusions, Rh antibody titrations on her blood will indicate whether or not she is sensitized. If antibodies active in albumin are absent late in the gestation period, the baby most likely will be unaffected. If these albumin-active antibodies are present early or late in the pregnancy and regardless of whether or not there is a rise in the titer, the first-born baby may be affected by hemolytic disease.

Albumin antibodies in the blood of 132 women who gave birth to babies affected with hemolytic disease of the newborn were studied by us during the first week after delivery. The data from this study support the view[1] that when the maternal titer reaches 1:64, there is an increased risk of unfavorable outcome to the live-born infant. However, there is such a wide range of variability in severity of hemolytic disease encountered at various maternal antibody levels (table 2) that the titer is not reliable as a specific prognostic aid in individual cases. Nor is a rise in albumin antibodies during the course of the pregnancy of an immunized mother a sure sign of an affected baby. We have studied two mothers in whom a rising titer of antibodies active in albumin was demonstrated, yet the baby in each case was Rh negative and unaffected by hemolytic disease. These exceptions are mentioned, however, only to define the limits of usefulness of titers. The exceptions do not alter the rule and when albumin antibodies are present in the maternal blood—and especially if the titer reaches 1:64—the physician should be alerted to the probability that an affected baby will be born and that he should make prepartum preparation for the treatment of the baby by exchange transfusion immediately after birth.

Knowing the mother is sensitized is always valuable, and, if the evidence of sensitization appears for the first time late in the pregnancy, the baby most likely will be affected by hemolytic disease; however, the disease may be so mild that it may be detected only by the Coombs' test. As will be discussed later, there is apparently an undefined characteristic of the mother, unrelated to her ability to produce antibodies, which is important in controlling the degree of affection in the infant.

Another problem in regard to antibody titers is worthy of mention. In those cases in which the mother has had previously affected babies and the husband is homozygous Rh

TABLE 2

VARIABILITY IN SEVERITY OF HEMOLYTIC DISEASE IN INFANTS NOW LIVING AND WELL WHOSE MOTHERS' RH ANTIBODY TITERS RANGED FROM 1:2 TO 1:260,000

INFANT	AGE ON ADMISSION *(Hours)*	MATERNAL RH ANTIBODIES*	EXCHANGE TRANSFUSIONS†
1	12	1:2	1
2	4	1:4	1
3	3.5	1:8	1
4	5	1:16	1
5	11	1:16	1
6	6	1:16	2
7	11	1:16	2
8	1	1:256	3
9	1	1:1024	1
10	4	1:1024	1
11	3.5	1:1024	1
12	24	1:4028	2
13	12	1:4028	2
14	4	1:4028	2
15	5	1:8192	2
16	3	1:16,384	1
17	4.5	1:16,384	1
18	12	1:130,000	1
19	3	1:260,000	2

*Antibody titers were done during the first week after delivery.

†The criteria for exchange transfusion were similar in all cases.

positive, a marked rise in albumin-active antibodies late in pregnancy may be of prognostic importance. This often prognosticates accurately a severely affected baby, and delivery of the baby as early as the thirty-seventh week may be indicated in an attempt to prevent a stillbirth. However, this should be done only if an exchange transfusion can be performed immediately after delivery.

Determination of antibodies active in saline solution has given some information which is useful in managing hemolytic disease of the newborn. Our experiences suggest that when such antibodies reappear late in the second or any subsequent pregnancy and are accompanied by a rising titer of albumin-active antibodies, this may indicate a new stimulation of antibody production by an Rh-positive baby. Whenever we have demonstrated such antibodies in the maternal blood, the baby of that pregnancy has been Rh positive. This must not be interpreted to mean that the absence of such antibodies in the presence of albumin-active antibodies indicates that the infant will not be Rh positive. In four of our cases, however, antibodies that are active in saline solution were not present late in pregnancy while albumin-active antibodies were present, and the infant in each case was Rh negative.

For the busy practitioner, antibody titrations appear to be of most value when used as follows:

1. If the mother is pregnant for the first time and has never had transfusions or injections of whole blood, no titrations are necessary during this initial gestational period.

2. In subsequent pregnancies, a titration is done early at the time of the initial examination to determine the existence or absence of iso-immunization. Another is done at about the thirtieth week and a third one at about the thirty-fifth week. If there are no antibodies present at the initial examination, the second test may be omitted. If antibodies are present at the initial examination, a sharp rise in the albumin-active antibody at the second determination indicates the possibility of a stillborn fetus and is, therefore, an indication for induction of labor at about the thirty-seventh week. This rule is emphatic if the husband is homozygous. The level of antibody at the third titration discloses late sensitization, which

rarely may be serious, and also will give helpful information about the probable necessity of immediate postnatal exchange transfusion.

In the multiparous woman who has had previously affected babies, there is no better guide in estimating how severely a subsequent infant may be affected by hemolytic disease than the history of severity in the prior born affected babies. In a nine year period we were able to collect data on 26 families with Rh ("D") and three families with hr ("c") incompatibilities. This involved a study of 129 infants in these family groups. Even though the severity of disease among siblings varied, those families whose first affected infant was only mildly affected tended to have mildly affected infants subsequently; those families whose first affected infant was severely affected tended to have severely affected infants subsequently. In only three families was a severely affected infant born after a mildly affected one. There were considerably more families with mildly to moderately affected infants than there were families with severely affected infants. These findings support the conclusion that the severity of hemolytic disease in newborn infants is a family characteristic and each family will tend to have successive similarly affected babies.

Even though the mother is Rh positive, maternal and fetal blood incompatibility cannot be dismissed entirely during pregnancy. In all of the maternal-fetal incompatibilities, the basic difficulty arises because the baby possesses a blood antigen that the mother lacks. Antibodies against this antigen are formed by the mother. When mother and baby are both Rh positive, the hr ("c") incompatibility is the most common Rh-hr problem. We have studied 11 instances of "c" iso-immunization in three families. The salvage of affected infants in these families was considerably lower than with the larger Rh group (450 cases). The lower rate was attributed in part to late recognition of the problem by the attending physician because the mother was Rh positive. A high survival rate can be obtained only by correcting this error and realizing that the "c" antibody often results in a serious form of erythroblastosis and that the management requires the same diligence as it does in cases of disease induced by the Rh antigen.

At the present time, the occurrence of hemolytic disease due to ABO incompatibility cannot be predicted during pregnancy even though the mother may previously have given birth to an affected infant. Determination of the parents' blood groups before delivery should not be neglected. ABO incompatibilities occur most commonly if the mother is group O and the infant group A. The disease occurs less frequently if the mother is group O and the infant B. Other ABO combinations producing disease are very rare. Methods of obtaining reliable prepartum serologic evidence of an affected infant have not been developed for ABO incompatibilities.

There have been many attempts to minimize the effects on the fetus of iso-immunization of the mother. Most of these attempts have been directed toward inhibiting production or neutralizing the effects of antibodies. These efforts have included the use of ACTH and cortisone in the pregnant immunized mother. There is no conclusive evidence of effective alteration of the production of maternal antibodies, their transfer to the fetus, or their effect on fetal red blood cells by these methods. There is evidence that the use of cortisone or ACTH during pregnancy may be dangerous to the fetus.[2-4] In our present state of knowledge, the administration of these agents to the pregnant woman for the purpose of influencing the effects of antibodies on the fetus is not justified and may be considered to be contraindicated.

If the study made prepartum indicates that an infant affected by hemolytic disease will be born, blood should be made available for exchange transfusion in the immediate postpartum period. Mother's blood, since it contains the same offending antibody as that present in the infant, is ideal for crossmatching. This procedure allows one to have blood ready to exchange immediately after birth. In our experience, group O blood crossmatched by the indirect Coombs' technic has always been safe. In the usual case of hemolytic disease, Rh-negative group O blood is used for the exchange transfusion. If the mother is Rh

positive, one is dealing, with rare exceptions, with an ABO or an hr "c" hemolytic disease problem, in that order. This can be predetermined in the case of "c" hemolytic disease by identification of the antibody in the mother's blood; but, if she is group O and her husband is group A or B, the ABO problem may also be present. Preparation before birth of O positive blood which is compatible with the mother's blood will be right for the baby in either case. This is because group O blood would not react with any immune anti-A which may have been transferred from mother to baby, and any group O blood which contained the antigen "c" would not crossmatch with the mother's serum. In using this prenatal preparation program, valuable time is saved and those severely affected babies with very low hemoglobin values and impending heart-failure may be given an exchange transfusion before heart-failure supervenes.

In this discussion we are concerned mainly with the management of hemolytic jaundice in the newborn. However, if we were always to wait for the appearance of clinical jaundice in an affected infant, therapy might not be initiated in time for optimal results. It is for this reason that prepartum anticipation has been stressed. Jaundice is not present at birth, and other clinical signs of hemolytic disease such as pallor or significant hepatosplenomegaly may be equivocal. These signs, of course, call for immediate investigation of cord blood in the same way as in those infants in whom the disease has been anticipated by prepartum testing. Cord blood drawn before the cord has stopped pulsating represents the infant's blood before it receives an autotransfusion from the placenta. There may be a difference of as much as 3 gm. in the hemoglobin value of cord blood and blood taken from the infant after the cord has stopped pulsating. However, if cord blood is not available, infant's blood may be used, and in either case the following testing should be done: blood grouping, Rh test, Coombs' test, determination of the value for the hemoglobin, examination of a blood smear, a reticulocyte count, and a determination of the serum bilirubin value.

If the infant is Rh negative and the Coombs' test is negative, there is no Rh-Hr problem. The Coombs' test is a test for sensitized cells and, therefore, is a test for hemolytic disease of the newborn. If properly done, it should be positive in almost all cases of Rh or "c" isoimmunization.

The Coombs' test indicates only that the infant is affected; it is not an indicator of the severity of the disease. It is of no value in therapeusis, and is usually of no help in evaluating the status of the patient after exchange transfusion. In cases of ABO hyperimmunization, it may be negative or slightly positive. If the infant is group A or B and the mother is group O, ABO hyperimmunization is possible.

Worthy of mention are several technical considerations necessary to obtain consistent results with the Coombs' test. If properly done, it is an extremely reliable test. Coombs' serum will combine with any globulin; therefore, all serum globulin must be washed from the plasma in which the red blood cells are suspended. Four washings are optimal. Unclean glassware may contain proteins which unite with Coombs' serum leaving none to react with coated red blood cells, and resulting in a false negative Coombs' test. Since proteins from the skin may cause the same type of reaction, the use of the thumb as a stopper when inverting the tubes with the test preparation should be avoided. Acid left in the tubes may leave the glassware serologically unclean and give a false positive reaction.

Anemia may occasionally be the most important single criterion for an exchange transfusion in the early neonatal period. Jaundice may not appear immediately, and the value for the serum bilirubin may yet be only slightly elevated. Anemia at birth in an affected infant, in the absence of blood loss, means rapid hemolysis and is followed by hyperbilirubinemia. Even though marked anemia at birth or shortly thereafter is serious since heart-failure and anoxia are potential hazards, we have found that the prognosis is good unless the value for the hemoglobin ranges near or below 5 gm. per 100 ml. Our experience includes two affected infants with hemoglobin levels of 4 gm. per 100 ml. within an hour after delivery. Both infants received a single

exchange transfusion immediately after delivery and survived without sequelae. Such babies will not tolerate procrastination. If the infant is affected (if the Coombs' test is positive), an exchange transfusion is indicated if the concentration of hemoglobin in the cord blood is 13 gm. or less per 100 ml. or if the concentration in the blood of the infant is 12 gm. or less per 100 ml. in the first 12 hours after birth.

Although anemia that occurs within the first 24 hours after birth many endanger life, even severe anemia that occurs later does not have the same implications. Anemia that occurs at this later time when the hemolytic process is subsiding may be only an indication for a simple transfusion.

Circulating nucleated red cells indicate the presence of an active disease process, but our experience indicates that the presence of such cells is not an unfavorable sign unless their number exceeds 375,000 per cubic millimeter of blood. After the first day of life, nucleated red cell counts have little significance.

In cases of Rh-hr hemolytic disease, examination of blood smears consistently reveals polychromatophilia and macrocytosis with varying numbers of normoblasts and erythroblasts. Examination of smears obtained from infants with ABO hyperimmunization reveals varying degrees of microspherocytosis, and this has been one of the mainstays in diagnosis. We have not observed any case of hemolytic disease due to ABO incompatibility in which less than 12 per cent of the red cells were microspherocytes; in the most marked example of microspherocytosis that we have observed in a case of this type, 32 per cent of the red cells were microspherocytes. It is well to keep in mind that, in some cases, congenital spherocytosis occasionally causes symptoms at birth and may simulate hemolytic disease of the newborn. Microspherocytosis is permanent in such cases, but it lasts only a few weeks in cases of ABO hemolytic disease.

An elevated reticulocyte count early in the course of hemolytic disease indicates an attempt to repair an active hemolytic process. In hemolytic disease due to ABO incompatibility, an initial elevated reticulocyte count may be especially useful because it may direct attention toward a hemolytic process before other signs become unequivocal. Irrespective of the cause of the hemolytic disease, during the first hours after birth the reticulocyte count very often helps in evaluating the severity of the hemolytic process, but it is not an infallible guide. Even though an active hemolytic process is usually indicated by a marked reticulocytosis shortly after birth, there may occasionally be marked hemolysis without a correspondingly elevated reticulocyte response. For example, infant A, at one hour of age, had a reticulocyte count of 18.2 per cent and a hemoglobin level of 7.25 gm. per 100 ml., while infant B, at six hours of age, had a reticulocyte count of 3.5 per cent and a hemoglobin level of 9.75 gm. per 100 ml. Both infants had an active hemolytic process, yet only in infant A did the reticulocyte count reflect the situation.

Determinations of the value for the indirect-reacting bilirubin in the serum at appropriate intervals form the *keystone of management* of hemolytic disease of the newborn. Hyperbilirubinemia is dangerous in the neonatal period, and its level cannot be estimated by the degree of skin jaundice, nor is it related proportionately to the level of hemoglobin or the number of red blood cells. This is illustrated by the cases outlined in table 3. Weech[5] demonstrated that, even with serum bilirubin levels above 12 mg. per 100 ml., occasional newborn infants do not develop clinical jaundice, and that a "critical level of serum bilirubin above which icterus is present and below which it is absent does not exist." Furthermore, it is imperative that serum bilirubin levels be followed as the patient becomes jaundiced. The degree of skin jaundice is not a safe guide. Also, anemia may not be present at any stage of the disease, and there is no consistent correlation between the presence of anemia or the severity of anemia and the degree of clinical jaundice. We cannot emphasize too strongly the folly of any attempt at following newborn jaundice through the use of hemoglobin levels or red blood cell counts, or both, to the exclusion of bilirubin determinations. There is no substitute for bilirubin determination.

TABLE 3

DISPROPORTION IN VALUES FOR HEMOGLOBIN AND BILIRUBIN

PATIENT	AGE *(Hours)*	HEMOGLOBIN *(Gm. per 100 ml. of blood)*	TOTAL SERUM BILIRUBIN *(Mg. per 100 ml.)*
Ste., 1953	5.5	4.25	5.6
Herg., 1953	5.5	9.0	10.2
Berg., 1952	5.5	10.0	14.4
Benj., 1948	5.0	16.5	23.2

Use of micromethods facilitates this program.

Our experience leads us to conclude that, if the value for the total bilirubin is above 4 mg. per 100 ml. of serum during the first six hours of life or above 10 mg. per 100 ml. within the first 12 hours, an exchange transfusion should be performed without delay. The average affected infant will have a serum bilirubin level of 5 mg. per 100 ml. or above within the first six hours of life, but he may have much lower levels and still be affected by hemolytic disease. In table 4 is tabulated a portion of our experience in this regard.

Except in cases in which the presence of hemolytic disease is detected late and in which the value for the serum bilirubin is above 30 mg. per 100 ml., there is no critical level of bilirubin which alone is an indication for more than one exchange transfusion. Exchange transfusion performed early, preferably within the first six hours after birth, may eliminate the necessity for a second exchange transfusion. In the newborn infant, a value of 20 mg. per 100 ml. for the indirect serum bilirubin is the critical level. The value must be kept below this level consistently in order to avoid brain injury.[6] Even if the value for the indirect serum bilirubin approaches 20 mg. per 100 ml. in an infant who is nearing one week of age, we feel obliged to reduce the hyperbilirubinemia as quickly as possible. Although the brain of older children is relatively resistant to a high concentration of indirect reacting bilirubin, there is suggestive evidence that the brain of these infants may be injured by high concentrations of bilirubin for a prolonged time.[7]

In the premature infant, the concentration of bilirubin should be kept considerably below 20 mg. per 100 ml. during the first days of life, since the brain of a premature is known to be more susceptible to the changes resulting in kernicterus than the mature infant's brain. Rarely is a premature infant's life in jeopardy because of the exchange transfusion procedure, but his damaged brain may be a life-

TABLE 4

INITIAL VALUE FOR SERUM BILIRUBIN IN NEWBORN INFANTS WITH HEMOLYTIC DISEASE*

AGE *(Hours)*	NUMBER	VALUE FOR SERUM BILIRUBIN *(Mg. per 100 ml.)*		
		Minimal	*Maximal*	*Average*
1 to 6	82	1.6	17.6	5.88
7 to 12	10	1.8	24.0	11.4
13 to 18	9	6.0	21.6	10.2
19 to 24	17	4.3	29.2	14.4
25 to 36	6	9.3	24.4	18.45

*The data in this table illustrate that although the average affected infant will have a serum bilirubin level above 5 mg. per 100 ml. within the first six hours of life, he may have much lower levels and still be affected by hemolytic disease.

long reminder to the physician if bilirubin encephalopathy is not prevented.

The indications for exchange transfusion in hemolytic disease of the newborn will vary somewhat with the problem at hand, but in full realization of our dogmatism we believe the following indications are valid for the immediate postnatal period for all Rh-positive infants if the Coombs' test is positive:

1. A past history of a sibling with kernicterus or a sibling severely enough affected to require an exchange transfusion. This does not apply to ABO incompatibilities.

2. Significant hepatosplenomegaly.

3. A hemoglobin value below 12 gm. per 100 ml. Exchange transfusion should not be postponed in markedly anemic infants with or without hydrops.

4. An affected infant born after less than 37 weeks of gestation. Because of the infant's prematurity, an exchange transfusion should not be deferred. The consequences of bilirubin encephalopathy far outweigh the dangers inherent in the transfusion procedure.

5. A concentration of serum bilirubin greater than 4 mg. per 100 ml. within the first six hours of life, 10 mg. per 100 ml. or greater at 12 hours of age, or approaching 20 mg. per 100 ml. at any time during the first week of life. These figures apply to the indirect-reacting portion of the serum bilirubin after the first three to five days of life. Total bilirubin may be used earlier.

For the infant who has survived the first 24 hours of life without treatment, hyperbilirubinemia becomes the sign of prime importance, and if the concentration is significantly elevated, bilirubin determinations are required every six to eight hours in order to detect the dangerous level at its inception.

The sole indication for a second or third exchange transfusion is increasing indirect hyperbilirubinemia. Rarely is a serum bilirubin determination helpful earlier than eight hours after an exchange transfusion. And, although the level at this time may indicate the need for a second exchange transfusion, more often it serves to establish a base for comparison with subsequent bilirubin determinations made at four to eight hour intervals thereafter. These repeated determinations need to be done day or night until the level begins to recede or until a second exchange transfusion is performed. Following a second exchange transfusion, the same follow-up program with serum bilirubin determinations is instituted. Because of the repeated determinations required, the micromethod which is done with blood obtained from the heel or finger tip is very helpful.

The presence of anemia without significant hyperbilirubinemia after the first day or two of life can readily be corrected by a simple transfusion. However, if hyperbilirubinemia accompanies the anemia, a second exchange transfusion is necessary.

Some infants with hemolytic disease will not require an exchange transfusion. If the indications are not present initially, observation of the infant for pallor, jaundice (scleral) and hepatosplenomegaly is mandatory at four to six hour intervals. Serum bilirubin, hemoglobin and possibly reticulocyte determinations at six to eight hour intervals for the first 36 to 48 hours of life will indicate the progression of the disease.

Finally, we must emphasize that there need be no completely hopeless situation in families with blood grouping incompatibilities. Between July 1943 and January 1955, over 450 cases of hemolytic disease of the newborn were seen by us in Denver Children's Hospital. Four hundred and fourteen of these cases were analyzed, and 29 families had more than one affected infant. In none of these families was there a hopeless situation. Even in the families with the history of severely affected infants, some of whom died within a few hours after birth, each family has at least one child born subsequently and affected by hemolytic disease who, because of diligent obstetric and neonatal care, is alive and well today. We believe that parents with a poor history of producing viable babies should not be advised to have no more children if they want more, nor should they ever be told that an abortion is indicated for any iso-immunization problem. If they have had two or more mildly affected infants, the chances are excellent that the next affected infant will be mild-

ly affected. If they have had a stillbirth, the situation is still not hopeless, even though the chances are increased that the next unborn child may be stillborn. If their affected child is born alive and survives the first 24 hours of life, his chances for full recovery are excellent with present day therapy.

Summary

Anticipation of jaundice during the first day of life is ideally carried out for the Rh form of iso-immunization as has been outlined. ABO iso-immunization, because of lack of definitive tests, cannot be accurately predicted. Also, for practical reasons, because of the frequency and the usual mildness of this form of the disease, the physician may best depend on careful observation in the nursery for the onset of jaundice; and, when early jaundice appears, he should apply the rules for following bilirubin levels. If serious ABO disease has been experienced in a family, one can prepare for transfusion antenatally as outlined in the paragraph on immunized Rh-positive mothers.

Other rare forms of neonatal jaundice may be anticipated. These include syphilis, viral hepatitis in the mother, acquired hemolytic anemia due to auto-immunization of the mother, familial hemolytic anemia and familial nonhemolytic anemia. Acquired hemolytic anemia due to auto-immunization gives a positive Coombs' test. A history of toxoplasmosis in the mother or galactosemia in a sibling may also be a clue. Although galactosemia is a rare cause of jaundice, it should never be forgotten, since with early and proper dietary management another tragedy of growth and of development can be entirely averted. "Physiologic" jaundice occurs after the first day of life. Sepsis, bile duct atresia, inclusion disease of infancy and hepatitis may cause early jaundice but do not lend themselves to prenatal studies. It should be remembered that, second to iso-immunization, sepsis of the newborn is the most frequent cause of first-day jaundice. All of these conditions with the exception of uncomplicated bile duct atresia may require exchange transfusion to prevent the development of kernicterus.

Jaundice appearing during the first 24 hours of life means hemolytic disease of the newborn until proved otherwise. We have stressed this disease because the sequelae of poor management are so disastrous and yet usually readily preventable. Still one of our most difficult problems in hemolytic disease is the prevention of death during the first 24 hours of life. Death occurs in those infants with marked anemia who supposedly die of heart-failure. Approximately one-third of our casualties were in this group. Immediate postpartum exchange transfusion is the best hope at present of saving more of these infants. Until clarification of the sequence of events in the pathogenesis of bilirubin encephalopathy is at hand, the problems of management of this group of infants must be based on the principle of the prevention of dangerous serum levels of indirect-reacting bilirubin or anemia, or both.

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Use of Temporary Cardiopulmonary Bypass in Cardiac and Aortic Surgery

REPORT OF 134 CASES

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DURING the past decade, progress in surgical treatment of diseases of the heart and great vessels has been rapid considering the technical limitations imposed by the necessity for continuous function of the heart during operation. Further significant expansion in this field, however, was delayed until means of treating intracardiac defects surgically under direct vision were available. Thus, the exciting development within the past two years of a temporary mechanical substitute for the function of the heart and lungs has removed a major barrier and provided a fresh and powerful stimulus for another period of progress and accomplishment undoubtedly beyond previous expectations.

Although other workers had performed experiments in temporary extracorporeal circulation, it was Gibbon[1] who focused wide interest on the problem. Since 1939 he has devoted much effort on an experimental level toward development of a pump oxygenator suitable for clinical application. Finally, in 1953, Gibbon[2] utilized his pump oxygenator successfully in a patient with interatrial septal defect. Meanwhile, Lillehei and associates[3] clearly demonstrated the clinical feasibility and importance of open cardiac surgery using controlled cross circulation between patient and a living donor who served as a biologic oxygenator of blood. Subsequently, Kirklin[4] and DeWall[5] and their associates demonstrated that mechanical oxygenators could be used

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effectively in an extracorporeal circuit, eliminating the need for a donor. Cardiopulmonary bypass by means of a completely mechanical device has since been utilized in a number of medical centers.

In our laboratory, experiments with pump oxygenators began more than two years ago. This report describes the apparatus currently in clinical use and analyzes briefly the results in 134 cases in which cardiac and aortic surgical procedures were performed by means of cardiopulmonary bypass. The operations were performed prior to April 1, 1957.

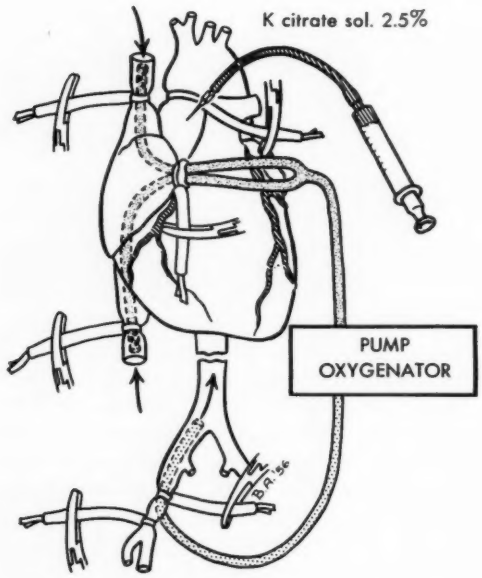

FIGURE 1. Diagram showing the method of cardiopulmonary bypass using a pump oxygenator system. Induced cardiac arrest is obtained by injecting solutions of potassium or acetylcholine into the ascending aorta so that intraventricular defects may be exposed in a quiet and bloodless field.

Method

Bypass of the heart is accomplished by removing venous blood from the venae cavae and pumping it through an oxygenator and back into the arterial system (figure 1). Plastic catheters are inserted through the right auricular appendage into the superior and inferior venae cavae for collection of venous blood, and a plastic catheter inserted in a femoral artery returns the oxygenated blood. The femoral artery and auricular appendage are repaired after the operation is completed. Two pumps are used to substitute for the right and left ventricles, and they must be equilibrated so that each delivers the same rate of flow. Usually the flow rates vary between 50 cc. per kilogram of body weight per minute for children and infants and 35 cc. per kilogram for adults.

To prime the pump and oxygenator, blood is freshly drawn and heparinized in siliconized bottles with 15 mg. of heparin per 500 cc. Heparin is administered to the patient in a dosage of 1.5 mg. per kilogram of body weight, and after the perfusion its effect is counteracted by giving protamine sulfate in approximately equivalent amounts.

Oxygenation of the blood in the extracorporeal system is accomplished in a stainless steel oxygenator of special design[6] (figure 2). This device operates on the bubble diffusion principle. The blood and oxygen are mixed in a vertical column and the foamed blood passes into a defoaming chamber where it contacts a stainless steel sponge coated with Dow-Corning Antifoam A substance. The liquid oxygenated blood then collects in a reservoir after passing down an inclined trough, and from this chamber it is pumped back into the patient's arterial system.

Cardiac arrest is induced, if necessary, as an adjunct to these procedures to produce a quiet, bloodless field which facilitates technical performance of surgical repair of the defect. After the venae cavae are occluded

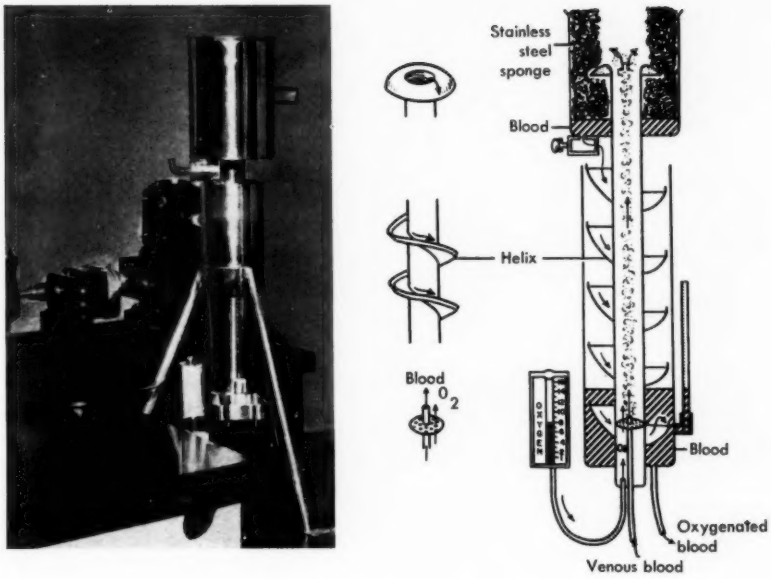

FIGURE 2. Photograph and diagram of stainless steel oxygenator used in cardiopulmonary bypass. This device, which has proved to be highly efficient, employs the bubble diffusion principle for adequate mixture of blood with oxygen.

and the cardiopulmonary bypass is functioning, the heart continues to contract forcefully because of the coronary circulation. Cardiac standstill is induced by occluding the ascending aorta and injecting a cardioplegic agent such as potassium citrate or acetylcholine into the ascending aorta until myocardial contractions cease and electrocardiographic activity of the ventricles disappears. Cardiotomy may then be performed and intracardiac procedures carried out under ideal working conditions. When the defect has been repaired the ascending aorta is reopened, the solution is perfused out of the coronary circulation, and myocardial contractions return without the use of stimulants.

Results

A total of 134 operations utilizing cardiopulmonary bypass were performed prior to April 1, 1957. The patients had various cardiovascular lesions, both congenital and acquired (table 1). In many instances, lesions were corrected which could not have been treated surgically by other technics. Many patients in advanced stages of cardiac decompensation with pulmonary vascular changes were operated on successfully and recovered completely. Thus the mortality rate of 23 per cent for the entire group is understandable and perhaps acceptable in evaluating the merits of a radically new method in surgery (table 2).

TABLE 1

CARDIOVASCULAR LESIONS IN 134 CASES OF CARDIOPULMONARY BYPASS

Ventricular septal defect	65
Atrial septal defect	23
Tetralogy of Fallot	8
Aneurysm, ascending aorta[7]	7
Aortic or subaortic stenosis	6
Atrioventricularis communis	5
Pulmonary stenosis	4
Single ventricle	2
Aorticopulmonary septal defect[8]	2
Transposition of great vessels	2
Total anomalous pulmonary venous drainage	2
Ruptured ventricular septum (coronary)[9]	1
Aortoventricular fistula (traumatic)	1
Ruptured tricuspid valve (traumatic)	1
Mitral regurgitation	1
Ruptured aneurysm, sinus of Valsalva	1
Aortic regurgitation (congenital)	1
Endocardial fibroelastosis	1
Mitral stenosis	1
	134

TABLE 2

MORTALITY IN 134 CASES OF CARDIOPULMONARY BYPASS

LESION	TOTAL CASES	DEATHS	
		Number	*Per Cent*
Ventricular septal defect	65	12	18.4
Atrial septal defect	23	2	8.7
Tetralogy of Fallot	8	3	37.5
Others	38	15	39
Totals	134	32	23

A more accurate and realistic evaluation of cardiopulmonary bypass may be obtained by considering the results in the 88 cases of ventricular and atrial septal defects that represent about 60 per cent of the series. For example, 12 of the 65 patients with ventricular defect died (18.4 per cent). Many of these patients, however, were small infants in critical condition at the time of operation. It is not surprising that among 23 patients less than two years of age there were seven deaths (30 per cent) contrasted to a mortality rate of 12.5 per cent for the 40 patients more than two years old. Yet the survival of 16 infants, some of whom weighed only 4 kg. at the time of operation, appears to justify operation even in infancy if circumstances indicate that the patient will not survive to a more acceptable age for surgical treatment.

Of particular importance in evaluating results of operation for ventricular septal defect is a consideration of pulmonary arterial pressure. Alterations in pulmonary vascular resistance in this condition have vital prognostic significance. In more than 30 per cent of the cases of ventricular defects in this series, cardiac catheterization disclosed pulmonary artery pressures in excess of 70 mm. Hg. In several cases it was more than 90 per cent of systemic arterial pressure, and in three the pressures in pulmonary and systemic arterial beds were roughly equal. A tendency toward reversal of intracardiac shunt was noted in some instances, with peripheral arterial oxygen saturation of 85 to 90 per cent, although frankly cyanosed patients with lesions such as Eisenmenger's syndrome were not selected for operation. Nevertheless the response of pulmonary arterial pressure to surgical repair of the ventricular defect was extremely gratifying, the maximal benefit in this respect occurring in cases in which the pulmonary pressure was greatest. Thus, where pulmonary pressure was greater than 70 per cent of systemic pressure the ratio decreased 50 per cent after closure of the defect.[10] Follow-up of patients with pulmonary hypertension who survived operation reveals convincing evidence of progressive decrease in pulmonary pressure at later cardiac catheterization, with roentgenographic evidence of decrease in pulmonary vascularity and of reduction in cardiac size (figure 3).

Cardiopulmonary bypass was employed to repair atrial septal defects in 23 cases, with two deaths (8.7 per cent) and complete closure of the defect in all instances. To our knowledge the lesion has not recurred in any case, although cardiac catheterization has been done postoperatively in less than half. One of the patients who died was a 50 year old woman in advanced stages of congestive failure at operation. She survived the surgical procedure, which consisted of repairing a massive atrial defect of the ostium primum type, but succumbed on the fourth day from acute heart block. The other death was from air embolism due to a technical error during operation. The 21 survivors in this group, however, have had a gratifying clinical response not only from a subjective standpoint but also from the evidence that cardiac function and cardiac size return to normal (figure 4).

Another advantage of cardiopulmonary bypass over other methods for repair of atrial

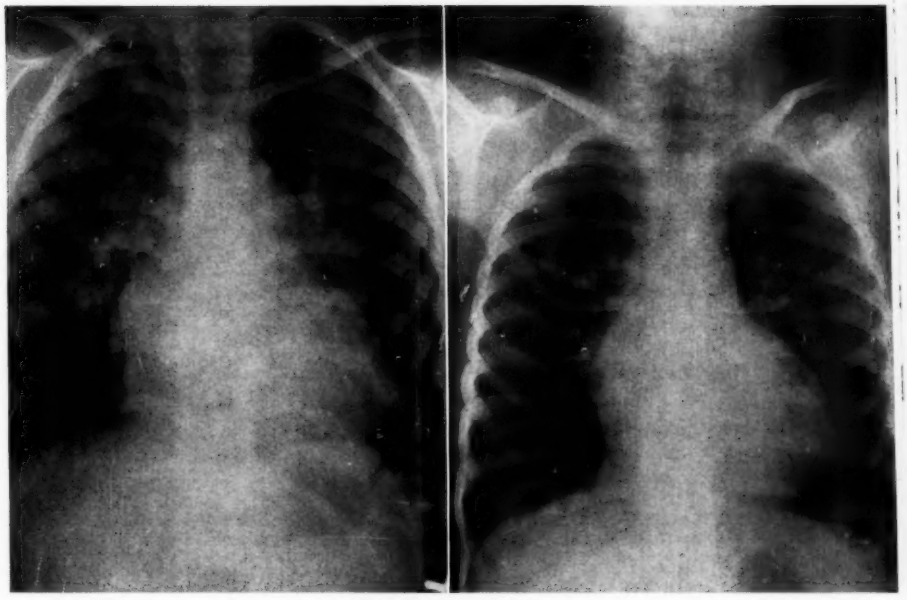

FIGURE 3. Roentgenograms of chest of five year old patient with ventricular septal defect before and five months after operation. During this period pulmonary artery pressure at cardiac catheterization fell from 90/50 to 36/10 mm. Hg.

defects is the fact that associated anomalies of pulmonary venous drainage may be corrected without difficulty. It has been possible, in cases of total anomalous pulmonary venous drainage into the right atrium, to transpose the interatrial septum so that the pulmonary venous ostia are replaced into the left atrium.

Open cardiotomy for repair of tetralogy

FIGURE 4. Roentgenograms of chest of 12 year old patient with large atrial septal defect, rheumatic myocarditis, and congestive failure made before and eight months after repair of the defect, showing striking decrease in cardiac size and pulmonary vascularity.

of Fallot was done in eight cases. Two of the patients were cyanosed and six were not. In fact, most of these cases were "atypical"; either the shunt at the ventricular level was balanced or a moderate left-to-right shunt existed. At present we continue to use the systemic-pulmonary anastomotic procedures for deeply cyanosed patients with tetralogy of Fallot because of the lower rate of surgical mortality and the generally satisfactory results.

Surgical treatment of lesions of the ascending aorta, including aneurysms and aorticopulmonary septal defects,[7,8] has produced gratifying results with use of the cardiopulmonary bypass method. Until now, lesions in these regions have presented a distinct technical challenge for surgical correction, but cardiopulmonary bypass enables the surgeon to isolate this vital area from the remainder of the vascular system for reconstructive procedures.

Summary

The recent development of pump oxygenator systems for temporary cardiopulmonary bypass has opened a new era in cardiovascular surgery, making possible the surgical treatment of many conditions previously considered incurable.

The technic of cardiopulmonary bypass is presented, and a new oxygenator is described which has distinct advantages over others used previously.

Results of operation in 134 cases are presented. This group included 65 cases of ventricular septal defect and 23 cases of atrial septal defect; operative mortality rates were 18.4 per cent and 8.7 per cent, respectively.

Factors determining survival such as age and degree of pulmonary hypertension are considered briefly. Further improvement in the technic of cardiopulmonary bypass undoubtedly will lead to more satisfactory results, but unless patients with advanced cardiac disease are denied possible surgical cure the risk of operation will remain largely unchanged for the present.

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Premedication for the Obstetric Patient

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ADEQUATE pain relief for the obstetric patient during labor presents a difficult and a challenging problem. The problem becomes especially complicated when one considers that all narcotic drugs currently in use, when administered to the point of sufficient analgesia for severe labor pains, also will depress the respiratory centers of mother and fetus. While the mother may be partially able to withstand this depression, the newborn infant is in many respects much less well prepared to do so.

Although infant mortality has been reduced by two-thirds during the past 40 years, there has been no equally significant reduction in deaths occurring during the first 24 hour period of life. Twenty-nine per cent of the entire first year's mortality occurs during this first 24 hour period. More than one-half of these deaths are related to problems of anoxia and abnormal pulmonary ventilation.[1] Herein lies our hope, since these conditions should be responsive, first, to adequate preventive obstetric measures and, second, to proper infant resuscitative technics.

In spite of good psychologic preparation, the patient in labor who does not need analgesic drugs is the exception rather than the rule. There are many advantages to be derived from a well-planned and carefully considered program of drug premedication. This program should aim for a reduction of maternal reflex irritability to its basal level without depressing the vital functions of mother or baby. As already noted, this objective may be difficult to accomplish. Furthermore, our plan must consider such complications as hemorrhage, toxemias and prematurity. Also, we must use agents that do not cause undesirable side reactions or alter the pattern of uterine

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Adapted from a presentation before the Continuation Course in Anesthesiology for General Physicians at the Center for Continuation Study, University of Minnesota, Minneapolis.

contractions. Finally, we must correlate the premedication plan with the plan of anesthesia to be employed during delivery.

Unfortunately, no single drug used for obstetric premedication meets all of these specifications. We must, rather, draw on a combined group of drugs, each of which possesses certain well-defined advantages. Among the wide gamut of drugs available for obstetric premedication are the belladonna derivatives, the barbiturates, the narcotics, the tranquilizers and the muscle relaxants.

Belladonna Derivatives

Of the two important belladonna derivatives, scopolamine has many considered advantages in obstetrics over atropine. Both drugs have a parasympatholytic action, producing a reduction in reflex irritability over the vagal pathway and a drying of secretions. These effects are essential in preparation for anesthesia. Scopolamine, moreover, has the further advantage of producing psychic sedation and allaying apprehension and anxiety. Its amnesic action is well established. Most important, these effects are produced without affecting the physiologic course of labor and without producing ill effects on the baby. It has even been shown that the direct injection of 5 to 10 mg. of scopolamine into the umbilical vein produces no untoward reaction in the infant.[2] One must, of course, point out the disadvantage of administering successive doses of scopolamine to a woman in labor, that is, its nonpredictability in producing muscular overactivity and extreme restlessness. This reaction occurs in about 10 per cent of patients and is further enhanced by the concomitant use of the barbiturates. Despite this particular disadvantage, scopolamine has occupied an important place in obstetric premedication ever since its introduction by von Steinbuchel in 1902.

Barbiturates

There are multiple advantages in the proper use of the barbiturates in obstetrics. These drugs possess both a hypnotic and an amnesic action, and they may also be helpful as anticonvulsants. However, their analgesic effect is negligible and they should not be used for this purpose. The chief disadvantages of the barbiturates include their unpredictable side effects and their depressant effects on the medullae of both mother and fetus; in some cases they even produce neonatal apnea. The number of available barbiturate compounds is legion; for example, pentobarbital sodium, secobarbital sodium (SECONAL®), amobarbital (AMYTAL® sodium) and thiopental sodium. In using the barbiturates we must consider both dosage and cumulative action in order to prevent asphyxia neonatorum and prolonged postpartum maternal depression.

It has been suggested that there exists a maternal placental barrier for barbiturates. Experimentally, however, all the barbiturates can be traced through the placenta to the infant. This placental transfer occurs even when very small amounts of barbiturates are used. In studying the placental transfer of various drugs, we found that following the intravenous injection of 150 mg. thiopental sodium to the mother, the placental or fetal level soon closely approximated that in the maternal blood plasma. The following data represent the means of 10 subjects studied.

PLACENTAL TRANSFER OF THIOPENTAL SODIUM

	PLASMA LEVEL OF THIOPENTAL SODIUM (*gammas per cubic centimeter*)	
	Initial level	Delivery of infant
Maternal side	8.9	4.3
Placental side	—	3.1

(The mean time from induction of anesthesia to delivery of infant was nine minutes.)

Other studies have demonstrated that barbiturates which are administered to the mother by the oral, rectal or intramuscular route soon appear in the fetal blood. Furthermore, after several hours, the fetus actually exhibits a pooling tendency for any barbiturate sedation given to the mother.[3] This is explained by the slower detoxication of barbiturate in the fetus.

A study carried out several years ago showed that Seconal and Amytal sodium were probably the safest of the barbiturates currently available.[4]

Narcotics

Morphine has been used for obstetric premedication for 60 years, but few clinicians now believe that it should be used past the first stage of labor, if at all. One study of premature babies showed that when morphine was administered within four hours of the time of delivery, the neonatal mortality rate was actually doubled.[5] Meperidine hydrochloride (DEMEROL®), which was developed as a synthetic substitute for morphine, has the advantages of shorter duration of action as well as a lessened respiratory depressant effect. However, it too will produce fetal depression, and the recommended single dose should not exceed 75 mg. It should not be administered within three hours of the expected time of delivery. It is claimed that alphaprodine hydrochloride (NISENTIL®), a narcotic introduced more recently, causes even less neonatal respiratory depression than Demerol. However, it too will cause some respiratory depression and must be administered with caution. A single dose should not exceed 30 mg. Apomorphine hydrochloride recently has been reintroduced as a hypnotic and an analgesic drug. It is suggested that when used in subemetic dosage (1 mg.) it exerts little depressant effect on either the mother or fetus.[6] This work is encouraging, but it is yet to be thoroughly established.

Two specific narcotic antagonists, NALLINE® and LORFAN®, developed within the past few years, have proved to be valuable additions to the armamentarium. These drugs may be given to the mother before delivery or intravenously injected directly into the umbilical vein of a depressed newborn infant, according to the following suggested dosage schedule:

	TO MOTHER *(Before delivery)*	TO INFANT *(Into umbilical vein)*
Nalline	5-10 mg.	0.2 -0.3 mg.
Lorfan	1- 2 mg.	0.05-0.1 mg.

Tranquilizers

This group of drugs, the phenothiazine derivatives, is the most recent addition to obstetric premedication. Two compounds which have achieved the greatest popularity are chlorpromazine hydrochloride (LARGACTIL®, THORAZINE®) and promethazine hydrochloride (PHENERGAN®). Both have multiple physiologic and pharmacologic actions, including the production of hypothermia and hypotension and antipsychomotor and antiemetic effects. It is important to realize that they also potentiate the action of the analgesic drugs used in obstetric practice. Thus far, no ill effects have been observed in the newborn infants when either drug has been administered intramuscularly to the mothers in a divided dosage of 25 mg. Of the two compounds, promethazine seems to be the more reliable and the more promising. Its hypotensive and cardiac accelerator action is also less prominent than that of chlorpromazine.

Muscle Relaxants

These substances have been used for several years as adjuvants to obstetric premedication and anesthesia. The administration of curare in repository form with the first onset of active labor has been recommended in order to reduce analgesic needs, accelerate the labor process, and reduce the number of episiotomies. A recent study of 200 patients showed no significant advantages to use of repository curare for this purpose.[7]

Muscle relaxants have been given intravenously during the third stage of labor in order to reduce the need for episiotomy and to facilitate forceps delivery. This technic has proved helpful, and clinical and laboratory studies in humans have demonstrated the nontransmission of d-tubocurarine across the placental barrier.[8] This property also permits the use of curare as an anesthetic aid during anesthesia for cesarean section. Laboratory evidence as to the transmission of other muscle relaxants across the placenta is conflicting, and at present we had best limit ourselves to using d-tubocurarine.

Conclusion

Obstetric premedication is a complex problem which does not lend itself to a simple routine. No single drug or even group of drugs provides a satisfactory answer to pain relief.

However, as more is learned about the specific actions of each drug, it is found that, when used in proper dosage and with due consideration for their effects, several drugs may be combined safely to provide the mother with adequate analgesia.

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Postgraduate Clinical NOTES

82. THE ART OF MEDICINE

In treating almost every illness there is need to strike a proper balance between science on the one hand and the art of medicine on the other; and much of the latter is to be found in the manner of the doctor by the bedside of his patients or in his surgery. It is true that, occasionally, either the art or the science of medicine may be paramount. When one is treating a mother who has lost an only child, or helping someone else in the last stages of cancer, compassion and sympathy may be all that really matter and science may hardly enter into the problem. On other occasions science and technique are all-important, as when a surgeon is doing a difficult operation, or a physician is treating an unconscious patient. By and large, we must agree with Dr. Geoffrey Barber when he says, "I would rather be in the hands of a man with an accurate knowledge of medicine, and with but little of the milk of human kindness, than in the care of the kindest man imaginable who didn't really know his job"; but luckily it is often possible to have the two together, because both the science and the art of medicine play essential parts in the care of nearly every patient. Not long ago a patient of mine had a baby girl who was born with a hare-lip and cleft-palate. We asked a famous plastic surgeon to talk to the mother a few hours after the child arrived, and I wish those who believe that modern science and a good bedside manner are incompatible could have heard what he said; the mother will remember it with gratitude all her life. No matter how much science develops during the next few hundred years, the need for the art of medicine will still be there. As Sir Arthur Hall wrote in 1941: "The need for it is as great today as it ever was, or ever will be, so long as human sickness continues."

John H. Hunt, The renaissance of general practice, *British Medical Journal*, May 11, 1957, pp. 1075-1082

Hypospadias—Complete Construction of Penis, With Establishment of Proper Sex Status

AFTER 13 YEARS OF MISTAKEN FEMALE IDENTITY

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In some instances of hypospadias, the infant has been mistakenly identified as female at the time of birth. Such mistaken identity may lead to accidental transvestism, but cross dressing does not imply perversion as long as the patient and his family are unaware of the error in identity. The recent report from a foreign country of the opposite of this situation, in which the external male genitalia were removed in a psychopathic transvestite, is unrelated to the present problem of mistaking a boy with hypospadias for a girl. The psychopathic transvestite and the questionable medical care given are mentioned only to distinguish this problem from the present one.

Mistaken identity in sex may last for varying periods, and the family is always subjected to considerable distress and heartache when it becomes necessary to change the sex of the child in the eyes of the world. Nevertheless, we have not seen a single patient who has not anxiously undergone the change from erroneous female identity to the correct male status, regardless of the degree of distress over the original error. The patients' families have also always welcomed the change. Because such an error can have an unpleasant ending and because the entire field of medicine is usually implicated in the eyes of the public when any medical error is made, we wish to report an outstanding example of complete construction of the penis in a patient, with establishment of the proper male sex after 13 years of mistaken female identity.

A patient was seen at the age of 13 years who appeared to be a girl insofar as social status and outward sex status were concerned. Enough questions had arisen, however, concerning the patient's normal feelings and reactions to warrant medical consultation. Biopsies of what had previously been considered part of the labia proved the tissue to be testicular.

On examination of the genitalia, pronounced deformity of hypospadias type was observed,

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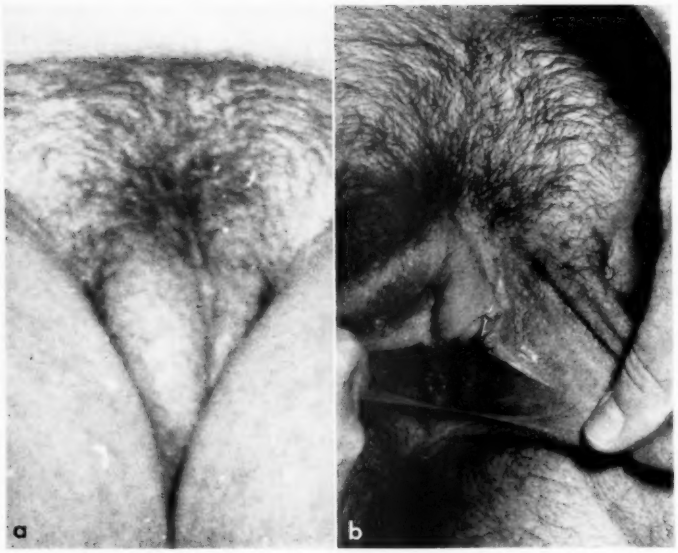

FIGURE 1a and b. Extreme deformity of genitalia of hypospadias type. Wide-open mucosal area had been considered as vagina, and phallic structure had been considered as clitoris. The structure previously thought to be labia was proved, by biopsy, to contain normal testes.

with hooding of the phallic structure and an open mucosal area, back toward the perineum, of sufficient width to suggest a rather open vagina. So severe was the deformity that the genitalia resembled those of a normal girl little more than of a boy. No evidence of a uterus or cervix was seen, and development of the breasts was that of an adolescent boy.

Consultations with the family doctor, the genitourinary surgeon and gynecologist resulted in the unanimous decision that a reconstructive operation should be done to establish the patient's proper male sex. The patient had his own ideas about being recast in life as a boy instead of a girl, even to selection of a name and a decidedly masculine program of activities that left no trace of femininity. These included being freed from his enforced transvestism, feminine name and other feminine attributes.

Repair of the deformity was done in two stages, which involved construction of the penis and scrotum. At the first operation, the lining of the blind perineal pouch was excised, and the opening was closed. Also at this time, the phallic structure, which formerly had been thought to be clitoris, was mobilized by opening the "hooded" fold which stretched across the dorsal surface. Release of this downward pull freed the phallus, and it was further released by an opening along the base of the

FIGURE 2. Functional penis has been constructed at proper level. Bifid scrotum has been united in normal relation with penis. (Photographs do not show the extent of normal appearance, but final substantiation of surgical construction of penis and rehabilitation of the patient is confirmed by his successful marriage.)

ventral surface as far as the blood supply would allow. The major portion of the defect of the phallus was then on the ventral surface, and this was covered with interdigitated flaps. Because of the depth of the cleft, flaps that were thick and would heal easily could be shifted from both sides. These lateral flaps were brought together over a catheter in the bladder and were carried out to the end of the phallus. The penile urethra was constructed in one operation, and the penis was constructed over the catheter. Urine was drained through the catheter without deflection of the stream.

At the second stage, further elongation of the previously constructed penis was possible by an additional opening at the base and subsequent coverage by local rotated and interdigitated flaps of the bulky tissue present. The testes, located in what previously had been considered to be the labia, were freed above and laterally and were then brought together in the mid-line lower down. In this way, the bifid masses were united below and in midline, and the scrotum was established in normal position.

Results of operation have been successful. The patient and his family dramatically and commendably shifted their feelings with the change in sex. The spirit shown by this patient and his family may provide an antidote to the unpleasant foreign reports of the opposite process in transvestism, in which a presumably normal anatomic situation was sacrificed surgically as a possible answer to a psychologic problem. The patient in this report has been successfully married, which confirms the establishment of proper sex status by surgical reconstruction.

Sex Chromosomal Determinations

This test can be used in instances of questionable sex with presumable reliance, although no large series has been recorded in which difficult decisions have been based entirely on this test. This work has been reported recently by Greenblatt and associates,[1] after the studies of Barr, Bertram and Lindsay,[2] Severinghaus,[3] Moore and Barr,[4,5] Marberger and co-workers,[6] Davidson and Smith[7] and others. The test is based on the observation that there is a mass of chromatin corresponding to the sex chromosome in most female cells that is seldom found in male cells. Scrapings taken from the mucosa of the cheek are fixed and stained for microscopic examination, which may determine the correct sex.

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Special Considerations in the Surgical Care of Infants

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THE truly effective management of any surgical problem in an infant or a small child embraces certain basic premises.

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1. One person alone must assume responsibility for care of the patient. The judicious use of capable consultants has long been a most acceptable medical practice. However, it is almost incomprehensible that a physician should accept the responsibility day after day for the surgical care of adults, making use of qualified consultants where indicated, and then, when confronted by an infant or a small child, turn himself into a surgical technician at the beck and call of a pediatrician. There can be little doubt that in a case of volvulus of the midgut the surgeon who prepares the patient for operation, corrects the condition, and follows the postoperative course is in the best position to know when to stop gastric suction, how much parenteral fluid and what type to administer, when to start feeding by mouth, and how to modify the oral feedings on the basis of the anatomic and pathologic changes encountered at operation.

2. Infants are not just miniature adults! They have different diseases, variations in physiology and relative differences in anatomy. Their responses are consequently varied and variable. Sir Lancelot Barrington-Ward phrased it most aptly when he said, "The adult may safely be treated as a child but the converse can lead to disaster."

There are certain facilities and equipment which a surgeon caring for infants should and has a right to expect. However, an ideal children's surgical service is rarely available except in a children's hospital which provides multiple other advantages to the ill and convalescing child, such as the playroom and the schoolroom.

Facilities

A separate and unified area of a hospital adapted to and staffed for surgical care is desirable (figure 1). Open, cubicled wards and

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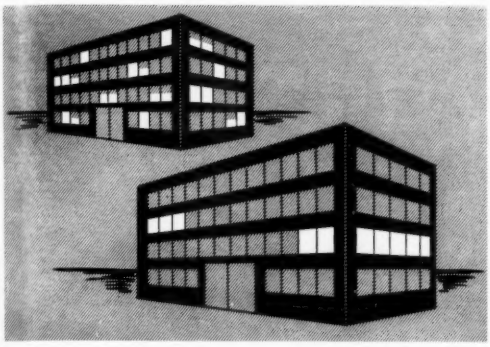

FIGURE 1. Separate, unified area of a hospital adapted to and staffed for surgical care is desirable.

FIGURE 2. Separate anesthesia induction area lessens trauma and promotes smoother course.

nursery areas, with their own treatment rooms, pantries and nurses' stations, make for greater efficiency and conservation of personnel and provide maximal nursing and house staff care as well as patient comfort and protection. There can be no argument that a separate area in which all patients are the responsibility of the same house officers, and in which regular rounds can be made with ease at least three times a day, provides better care for these children.

Regular visiting hours expedite the care of larger numbers of patients by smaller house and nursing staffs and in general result in better patient care and hospital public relations. Those patients who do not have visitors are taken to a playroom or amused by volunteer workers at the bedside.

Location of the operating suite (with induction room, recovery room and central supply rooms) in a remote section of the hospital—preferably on another floor—has many advantages. It not only eliminates almost completely the "tagging along of parents" but also removes a major portion of the unpleasant aspects of surgery from the open ward area. An induction area separate from the wards and outside the actual operating room, with its lights and instruments and noises, promotes smoother, less emotionally traumatic anesthetic induction (figure 2). In a like manner a well-equipped, well-staffed recovery room with an intercom to the main operating suite enables the responsible anesthetist and surgeon to supervise the critical period during recovery from anesthesia (figure 3).

Sympathetic and cooperative nursing can relieve much of the terror of a surgical experience. With a little extra effort it is possible for the admitting nurse on the ward to accompany the small child to surgery, be with him during induction, be present in the operating room, care for him in the recovery room, and return with him to his own cubicle. This nurse, sharing with him the terror and bitterness of the dreaded unknown, can comfort and reassure the worried infant.

Equipment

The ISOLETTE® is probably the greatest single aid available in the surgical care of the tiny infant (figure 4). Its many advantages

FIGURE 3. Well-equipped, well-staffed recovery room permits supervision during critical postoperative period.

FIGURE 4. The Isolette is probably the greatest single aid to surgical care of tiny infants.

are too numerous to relate. Suffice it to say that as a home for the infant it provides well-regulated warmth and humidity and economical oxygen concentrations in a convenient working area for nurse and doctor. It affords unsurpassed visibility for observation of respiration and physical activity, and convenience of handling, since no clothing is worn. The isolation of the patient from his neighbors and from the contaminated or ailing doctor or nurse is an additional safeguard. Intravenous cutdowns, weighings, spinal taps and other procedures are all possible within its protective shell. Frequent use of the oximeter to insure maintenance of proper oxygen concentrations below 40 per cent is essential. The development of retrolental fibroplasia associated with overoxygenation is an unnecessary and preventable complication.

The use of some form of intermittent nasogastric suction has proved superior to any continuous suction apparatus. The succulent mucous membrane of the infant stomach is easily drawn into all the holes in the nasogastric tube, and with constant suction this renders the tube almost completely ineffective within seconds as well as producing multiple small areas of ecchymosis and in some cases ischemia of the gastric mucosa. Interrupted suction reduces the irrigation of the tube to a practical working schedule. The apparatus shown in figure 5 sucks for 25 seconds, shuts off for 5 seconds, and restarts with a pressure of either 90 or 120 mm. of water.

In tiny infants the use of a water-trap type of chest drainage has long been recognized as unsatisfactory, and the more strenuous forms of motor suction have been equally unsuitable. A standard water-column type of control valve seems to be the best available solution. It protects the infant against power shortages and fluctuation in suction strength and provides simple control of pressure (figure 6).

Routine operating room use of a telethermometer enables the alert anesthetist to follow the patient with constant rectal temperature readings. It is then possible to employ the necessary measures to control body temperature. The circulating fluid mattress provides a single convenient way of raising or lowering body temperature as needed (figure 7).

FIGURE 5. Intermittent nasogastric suction is superior to continuous suction.

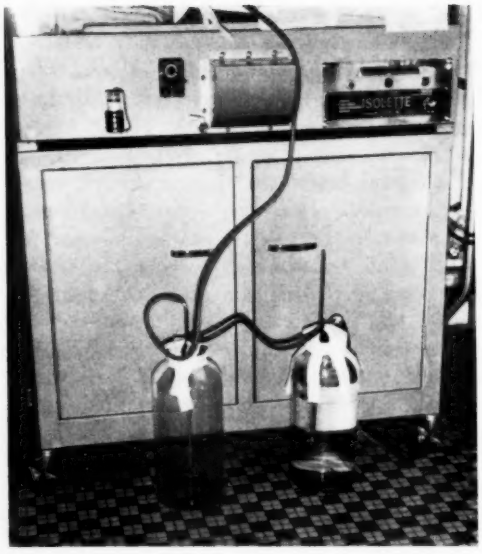

FIGURE 6. Standard water-column type of control valve seems best for chest drainage.

Newborn "Vitality" Curve

In surgery of the newborn infant it is well to bear in mind the poorly understood phenomenon which may be referred to as "vitality." At birth, the infant has already demonstrated a strong desire to survive, and with a few hours of rest this vitality appears to increase (figure 8). The vitality curve reaches a peak apparently on the third to sixth day, and following this there is a definite slacking-off, a "toboggan slide" appearance, for the next two to three weeks. Then the "reserve" strength and endurance gradually increase and the vitality regains its former high level at about six weeks. While it is obviously impossible to plot any infant's exact curve, this fluctuating graph serves as a basic guide in avoiding elective procedures until all possibility of urgent, emergency surgery is passed. By the same token it is helpful in scheduling urgent surgical treatment at a more optimal period.

Parental Influence

When dealing with infants, either surgically or medically, the physician must maintain a proper child-parent perspective. Care of the ill infant is always the prime objective. Sympathetic understanding of the parents' anxiety and a simple, honest explanation of the infant's condition will pay dividends in cooperation and conservation of the doctor's time. On the other hand, parents must not, through oversolicitude, hamper the proper care of the infant. The acutely ill surgical patient requires constant close supervision by trained personnel. The interference, help and solicitude of worried parents practically always leads to omission or modification of some part of the routine surgical care which is accepted as the best system of restoring the child to health. Every honest physician will admit that circumstances "nonmedical" in nature influence his handling of infants and parents. There can be

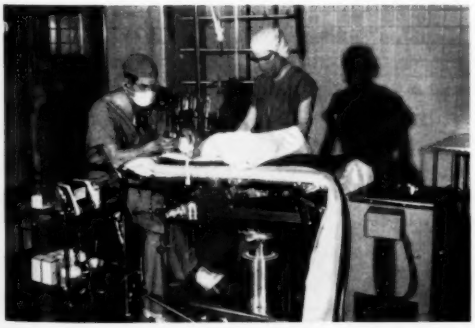

FIGURE 7. Circulating fluid mattress permits raising or lowering of body temperature.

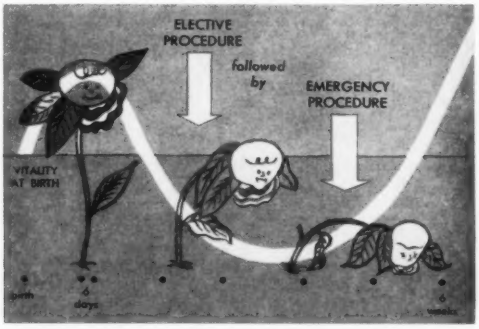

FIGURE 8. "Vitality" curve in newborn period must be borne in mind in scheduling operative procedures.

FIGURE 9. Exclusion of a young patient from conversation may induce apprehension.

no greater tragedy or source of guilt than the knowledge that a patient has suffered because of this failing.

Nurses who are not trained in the care of the surgical child constantly question the necessity of such measures as arm and leg restraints, catheters and gastric suction tubes,

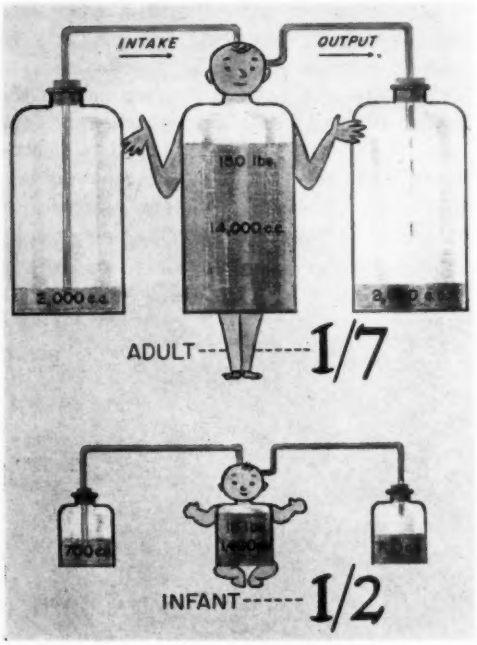

FIGURE 10. Relation of total intake and output to extracellular fluid volume in adults and infants.

all because of their personal contact and emotional tie-up with the patient and his relatives. House officers, on the other hand, tend to forget that the medication administered by intramuscular injection during the acute phase of an illness could often be stopped or changed to the oral route several days sooner—possibly an innate resistance to the suggestions of nurses or parents.

The policy of making microscopic diagnoses of masses, lumps and bumps in children within 24 hours after admission has relieved the minds of parents innumerable times by ruling out malignancy. But definite diagnosis, by confirming their worst fears, quickly may eliminate the possibility of the final outcome being attributed to inefficiency or procrastination on the part of a hospital staff.

There are some conditions in which the actual health of the infant may be secondary to the parents' peace of mind. The hopelessly advanced malignancy is an example.

The concept that a doctor who accepts a child as a patient accepts also the parents is above question. Parents who submit their child to operation have every right to expect an *unhurried* interview with the surgeon (not the referring physician) during which they receive a satisfactory explanation in simple lay terminology. They are no less entitled to talk briefly with the surgeon immediately after the operation to obtain his reassurance and outline of the future course.

While tiny infants are oblivious to the mysteries of "grand rounds," older tots of two to four years are all eyes and ears. They absorb all the gestures, long words and solemnity of the discussion. In order to avoid such unconscious torturing of the patient it is well to cultivate the habit of speaking in an open and matter-of-fact way. The youngster who is included in the conversation rather than excluded by whispering and poorly veiled muttering is certainly less apt to misinterpret the gravity of his prognosis (figure 9).

Extracellular Fluid Volume

The traditional comparison of the intake and output of an adult and an infant with extracellular fluid volume bears re-emphasis

(figure 10). The fact that an infant exchanges or replaces one-half of his extracellular fluid volume each 24 hours as compared with the one-seventh part exchanged by the adult must always be kept in mind. The overworked nurse who has too many babies to feed is apt to become impatient with the "poor nurser" and thus punish him with shorter feeding time and consequently an inadequate intake. The adult-trained anesthetist who writes "N.P.O. after midnight" from habit cheats the infant scheduled for 8 A.M., to say nothing of the one scheduled for 10:30 or 11:00 A.M.—or "when the rest of the schedule is finished," which is apparently what "T.F." (to follow) means.

Intravenous Fluids

Because of the small extracellular fluid volume of the infant, any rapid administration of intravenous fluid may result in disaster. With the spasm of the vein following a cutdown or even venipuncture, and the associated increase of intrathoracic and intra-abdominal pressure secondary to crying and straining either in the treatment room or during induction, the carefully regulated drip eventually becomes a rapidly flowing stream when the infant falls off to sleep.

In order to avoid such accidents it is wiser to resort to less convenient burets with their objectionable qualities (increased chance of contamination, increased workload for nurses) and limit the fluid orders to eight hour periods (figure 11). Thus the patient is re-evaluated by a doctor *at least* every eight hours, and the worst accident possible would be that one-third of his daily fluids would be administered too rapidly. This also eliminates the use of "markers" on large bottles intended to warn the floor nurse to discontinue the fluid at that point and, of course, the room warming of a large bottle of blood each day during the administration of small amounts of blood by transfusion. The practice of using a filter on *all* burets eliminates the chance of administering unfiltered blood. When the fluid requirements of the period are met, the plugging of the tube with a saline syringe rules out the dangerous order "Continue slow drip to keep intravenous open."

It has long been the practice in performing venous cutdowns to thread the largest possible polyethylene tubing into the vein by the simple expedient of stretching the vein over the beveled tip and gradually working it on (figure 12). We now believe that a small tube which will drip clear fluids but may require some pumping of blood is quite adequate. This method seems to reduce the incidence of chemical phlebitis or ischemic phlebitis, or both, and to prolong the period of effective use of the cutdown noticeably. Whether this is due to quicker dilution and mixing of fluids or to the bathing of the vein wall with blood is problematical.

A well-padded cutdown board for fixation with a piece of sponge rubber beneath the bony prominence is essential in the operating room (figure 13). The practice of removing the board after surgery and replacing it with an elastic bandage permits freedom of han-

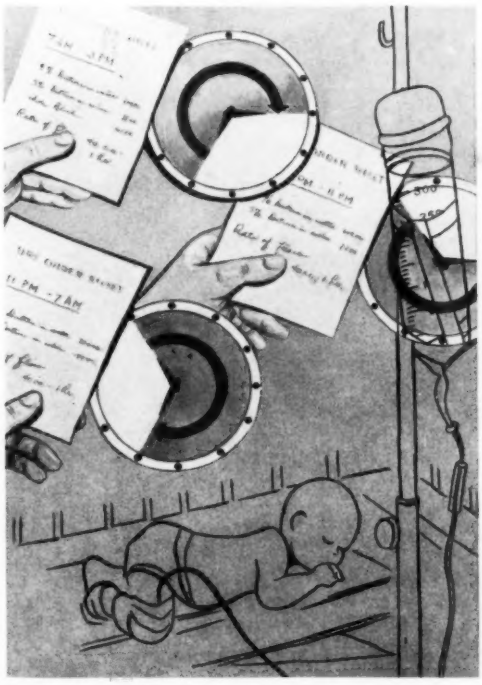

FIGURE 11. Limiting orders for fluids to eight hour periods and using filtered burets make for safer administration of intravenous fluids.

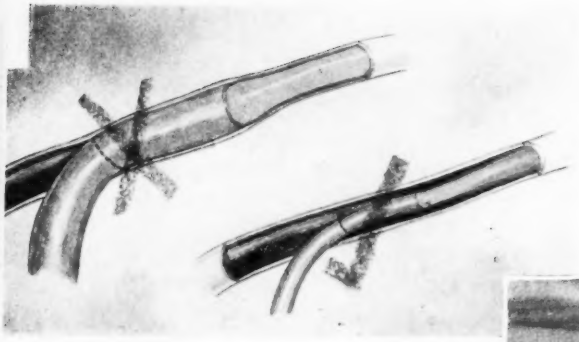

FIGURE 12. Smaller tubing for venous cutdown seems to reduce incidence of phlebitis and prolong period of effective use.

FIGURE 13. Well-padded cutdown board is essential in the operating room.

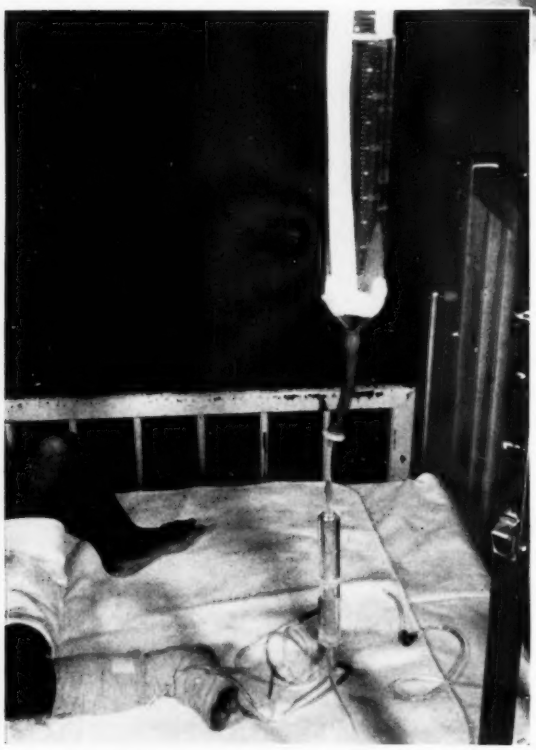

FIGURE 14. Board removed after surgery and replaced with elastic bandage.

dling and of motion of the extremity and the patient (figure 14). It is quite possible that this routine has also prolonged the usefulness of the cutdown.

Fluid Balance

In evaluating the fluid requirements of infants the usual signs of urine output or number of voidings, amount of saliva or moisture of the tongue and lips, skin turgor, and consistency of stools are all employed. However, in the presence of diarrhea, vomiting or an ileostomy, frequent weighing of the infant and weighing of soiled dressings on a dietetic scale are much more accurate methods of keeping up with fluid losses. The use of the Mikulicz spur-type ileostomy or exteriorization has become almost routine in our acutely ill infants with either an ileal atresia or an irreducible intussusception. Dr. Edward Brenner[1] phrased it most aptly years ago when he said, "The child's body is no place for heroic surgery." Careful attention to fluid balance and early application of the spur-crushing clamp have dispelled the myth of the intolerable ileostomy.

"Tricks of the Trade"

In handling infants surgically as well as medically, the little "tricks of the trade" make a great deal of difference. Any institution planning to care for a considerable number of infants must be geared to render service—24 hours a day and within 24 hours—to avoid unnecessary hospital days. The x-ray department must develop the quality of patience and must repeat films and studies until the desired information is obtained *without* the cooperation of the infant.

Nurses and doctors alike must cultivate the art of examining and observing, in a manner similar to our veterinary colleagues who do not depend on subjective symptomatology but must rely solely on keen clinical observation and patience.

The laboratory must acquire the knack of performing studies on inadequate amounts of blood, employing microscopic methods so that a barrage of blood chemistries and cultures will not make blood loss a real threat, or delay treatment!

All departments and personnel must acquire "the touch" (figure 15).

Both preoperatively and postoperatively, the surgeon cannot afford to overlook even the smallest, most inconsequential fragment of therapy. By and large, all doctors remember and employ the big, important items of their therapeutic armamentarium. However, in dealing with the critically ill infant, one more bit of attention may tip the scale in the right direction. Whether it be the use of blood and plasma in frequent small amounts, gamma globulin, or vitamins, the changing of the infant's position every hour, irrigation of a nasogastric tube, or some other "minor" detail, it is the sum total of these attentions which saves the tottering case (figure 16).

Scheduling and Preparation for Operation

Perhaps one of the greatest wrongs done the infant who requires surgical treatment is the sandwiching of the procedure between "important" cases or, even worse, the scheduling of the operation at the end of a long list of adult cases which drag on and on and eventually lead to cancellation of the last case.

FIGURE 15. All personnel must acquire "the touch."

The preparation of a child and his parents for surgery should follow a definite plan, which should be altered *only* by the demands of the case itself. Delays of any type, whether in terms of minutes or days, tend to defeat the aims of good patient care in cases of small children (figure 17).

Infants and small children are by nature early risers and usually awaken smiling and

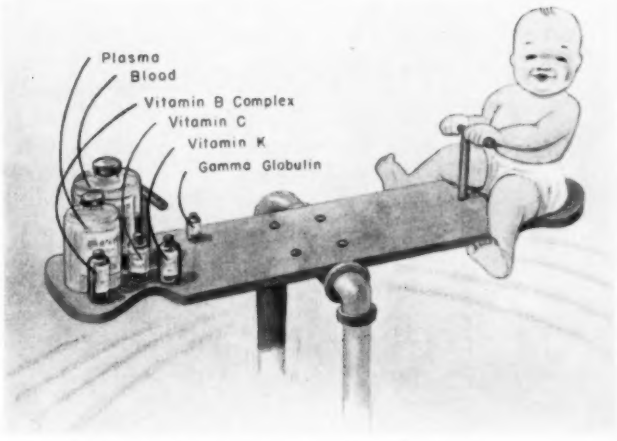

FIGURE 16. Seemingly minor details may tip the scale in favor of a critically ill infant.

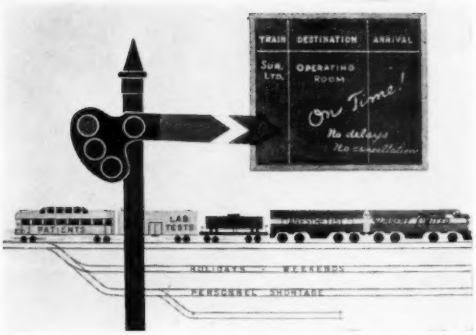

FIGURE 17. Preparation for operation should follow a definite plan, without delays.

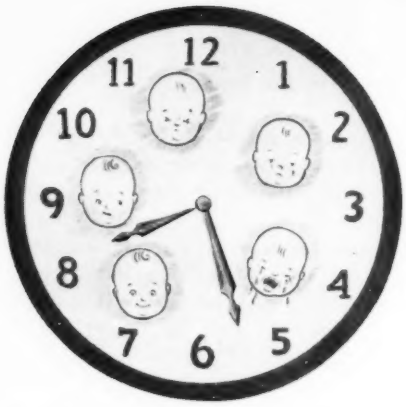

FIGURE 18. Morning scheduling of all operations on infants and small children is preferable.

hungry. Any delay in feeding, especially when augmented by the anesthetist's "secretion-drying" medication, rapidly leads to a loud demonstration of discontent, dissatisfaction and downright displeasure, all of which in turn lead to air swallowing, elevated metabolism, sobbing respirations and all the concomitant drawbacks to a smooth surgical procedure. While all children cannot be operated on at 8 A.M., it is certainly preferable to arrange for morning scheduling of all infants and small children whenever possible (figure 18).

Once the infant is delivered to the operating room, the personal skill, education and experience of the surgeon are all-important. There are no substitutes. Probably the greatest shortcoming of surgeons in the treatment of infants is a lack of knowledge of embryology. Here the information must be ever present, since there is no time to refer to textbooks. Any pertinent observations must be made almost automatically and these must be recorded *immediately* afterward in an operative note which will be not only available but also informative in future years (figure 19).

The care of the sick infant will never be the responsibility solely of specialized pediatric surgeons except in a few medical centers and children's hospitals. It is and will remain the responsibility of the general surgeons. The pediatric surgeons have pointed up the fact that the *mere age* of a patient is no justification for poor surgical results and a high rate of mortality.

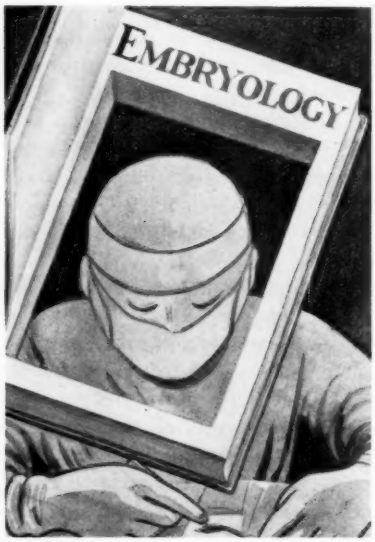

FIGURE 19. Lack of knowledge of embryology is probably the greatest shortcoming of surgeons in treatment of infants.

ACKNOWLEDGMENT

Illustrations are by the Visual Education Department, University of Louisville School of Medicine, Louisville, Kentucky.

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Diffuse Otitis Externa and Its Effective Treatment

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RECENT articles[1,2] about otitis externa have repeatedly emphasized that this diagnosis has become a receptacle for a variety of ear conditions. This confusion is apparently compounded by the ready blending of different forms of infectious and noninfectious dermatitis. Clinically, dermatitis of the external ear canal may result from infection, trauma or local dermatologic causes.

For instance, in children a characteristic dermatitis of the external ear canal often follows or coexists with local infection resulting from purulent middle ear discharge. Similarly, infection in the external ear canal may precede or result from dermatitis when the etiologic agents are fungi, streptococci or other pathogenic organisms. However, local infection usually follows dermatitis in the external ear when seborrheic, psoriatic or allergic manifestations are apparent on other parts of the integument.

Differential Diagnosis

Overlapping symptoms also require differentiation. Thus, intense itching is common in acute and chronic dermatitis as well as in fungal infections of the external ear. Pruritus also may appear in mild cases of herpes, but pain is more common. Persistent pruritus of varying intensity is also characteristic of "chronic" ears, along with tinnitus and hearing impairment which may result from the filling of the ear canal with dry scales and detritus. Pruritus without any local physical signs has been reported,[3,4] and may be very puzzling. However, some unsuspected systemic condition such as diabetes mellitus, hepatic disease, lymphoblastoma or allergy may be responsible. Psychogenic pruritus is also possible, and, like pruritus of any other etiology, can lead to secondary infection. Itching always incites scratching; and fingernails, toothpicks, matchsticks and hairpins can erode the skin and introduce infection in the ear canal.

Infection in the ear canal may take the form of a furuncle or pustule, i.e., circumscribed otitis externa, or it may extend along the entire length of the canal, i.e., diffuse otitis externa. Intense pain is the characteristic complaint with either type of infection. In fact, in the more deep-seated forms of diffuse otitis externa, aural pain and headache may be extremely severe. Comparable pain may occur in local erysipelas, which has a sharply circumscribed appearance differentiating it from diffuse external otitis and acute local dermatitis. Similarly, intense pain may occur in aural herpes zoster, which is accompanied by high

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fever and symptoms of general illness that also help differentiate it from blistering forms of acute otic dermatitis.

After adequate local cleansing, otoscopy with the smallest available speculum will permit the visualization of the tympanic membrane and help establish the diagnosis. For this reason, otoscopy should not be neglected even in the most obvious case. This procedure can also disclose the presence of macroscopic fungal masses and the typical appearance of bacterial infection in the ear canal. The character of the discharge present is also suggestive of the dominant microbial agent. A gray or yellowish-gray purulent discharge may be seen in *Pseudomonas* infections. A green or greenish-yellow purulent discharge may occur with hemolytic *Staphylococcus* organisms. In regard to fungi, *Aspergillus* may cause a discharge with a musty odor; *Candida* may cause a whitish, flaked discharge. An adhesive, mucoid discharge has been seen in *Phytomonas* infection of the canal.[5]

Etiologic Relationships

At present, the etiology comprises the coincidental association of several physical, climatic and microbial factors which show a recurrent pattern in the anamneses of patients and in published reports.

Prior to World War II, otitis externa was considered largely fungal in origin. The increased incidence of the condition among armed personnel in the tropics helped establish the role of bacteria. Syverton, Hess and Krafchuk[5] observed bacterial infection in 75 per cent and fungal infection in only 25 per cent of cases of diffuse otitis externa. *Pseudomonas* was present in 66 per cent of cases and *Staphylococcus aureus hemolyticus* in 18 per cent. *Pseudomonas* was the only organism recovered from infections in six ears, and was found mixed with normal flora in 27 of 72 ears examined. Senturia and associates[6,7] also confirmed the dominance of *Pseudomonas* bacilli in diffuse otitis externa, and reported the persistence of virulent forms in cases which had failed to improve with treatment. Since then the importance of *Pseudomonas* organisms in cases of diffuse otitis externa infections has gained constantly wider recognition.

The possible introduction of these microbes by scratching or ear-picking has already been mentioned. However, their presence may also result from the exposed position of the ear. The tortuous cavernlike structure of the canal and the components of the cerumen could favor microbial growth.[5,8] The change from the normally acid pH toward the alkaline in dermatitis and infections of the canal also favors bacterial proliferation.[9]

The greater incidence of the condition in hot and humid weather following frequent showers and swimming is generally accepted.[1-10] Senturia and Carruthers[7] believe that heat and moisture may favor edema and deprive the canal of protective secretions by compressing the excretory ducts of the local glands. The subsequent swelling and inflammation could lay the groundwork for fungal or bacterial infection.[11]

However, the role of these factors, per se, is cast in doubt by the recent work of Perry and his associates.[11,12] They reproduced the effects of heat and humidity in the canal by plugging the ears for three to four weeks without inducing external otitis. The resulting macerated condition healed spontaneously in all subjects. They also seeded virulent *Pseudomonas* organisms in the ears of seven subjects, one with a dry, scaling chronic ear, without recovering any organisms a week later or subsequently inducing the condition.

Evidently, the true mechanism for the onset of diffuse otitis externa remains to be demonstrated. However, from a practical point of view, the commonness of pain as the presenting complaint indicates that infection is usually present by the time the majority of patients seek the physician's help. Since this is the case, the general practitioner can only try to alleviate the pain as quickly as possible and to treat the infection with the most effective means available.

Treatment—Theory and Practice

After basic diagnostic considerations and local examination, cleansing and treatment may be undertaken. Although bacteriologic diagnosis is theoretically desirable in every

instance, the average patient who comes to a general practitioner because of an earache will not readily accept the delay, inconvenience and extra cost.

In practice, treatment with an agent whose established use is confined to local application is usually safe and satisfactory. I have had experience with polymyxin B and undecylenic acid individually, but during the last four years I have had better results than ever before with a special aural preparation combining neomycin and propionic acid. Specially formulated to assure effective concentrations in the small dosage used in the ear, this preparation known as OTOBIOTIC®* is generally available on prescription.

Otobiotic is a nontoxic, nonirritating solution with a pH of 6.5, which has a physiologic action in the ear. It contains 3.5 mg. neomycin (as sulfate) and 50 mg. sodium propionate per cubic centimeter in an autogenously sterile hydroalcoholic vehicle. The spectrum of neomycin includes gram-negative as well as gram-positive organisms. It is especially useful locally in otitis externa because of its effectiveness against the two most commonly encountered bacteria in this condition—*Ps. aeruginosa* and *Staph. aureus hemolyticus*.[13, 14] The acid derivative of sodium propionate is effective against certain gram-positive cocci and is especially useful for the destruction of all fungal invaders. Otobiotic appears to be a highly rational formulation for the treatment of all forms of infected otitis externa.

After the ear is cleansed by either irrigation with tap water or tip suction followed by the application of small cotton-tufted applicators, a cotton tampon soaked with Otobiotic is inserted into the canal. The patient is instructed to keep this tampon saturated with Otobiotic for a 48 hour period and then to remove it. If the symptoms have not completely subsided, the patient is requested to return, and the treatment is then repeated. However, if the first 48 hour course of treatment is successful, the patient is instructed to instill two or three drops of Otobiotic into the affected ear three times a day for three days, and then to use the drops only at bedtime for four days. Patients are advised to discontinue this medication if they are symptom-free and comfortable at the end of this time.

As a routine measure against pain, I prescribe 10 gr. of aspirin and 0.5 gr. of codeine. If pain is not diminished or made bearable, a more potent analgesic may be prescribed. The patient is also advised to use cold ice bag applications over the ear to facilitate pain relief. Heat—particularly moist heat—should not be applied locally.

Results of Treatment

Of 713 patients treated successfully by this method over a four year period, 347 required only one office treatment; 237 required two office visits; 87 required three treatments, and 32 required four office treatments. All of the patients in the remaining group who required more than four office treatments had conditions complicated by perforated eardrum and previous chronic otitis media. However, the ears of these patients also became dry and free from discharge, with marked improvement of the chronic otitis media when treatment with Otobiotic was finally terminated.

*A product of White Laboratories, Inc.

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Management of Idiopathic Thrombopenic Purpura With ACTH, Cortisone and Splenectomy

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In the past few years our knowledge of the mechanism and treatment of "idiopathic" thrombopenia (thrombocytopenia) has increased remarkably.[1-3] The disease is a hemorrhagic disorder associated with a reduction in the number of circulating platelets, a normal or an increased number of megakaryocytes manifesting certain cytologic features, and an absence of splenomegaly, and usually responding to either steroid therapy or splenectomy.

There is evidence to support an immunologic mechanism in the pathogenesis of idiopathic thrombopenic purpura (ITP). Indeed it has been suggested that the term "immunoallergic thrombopenic purpura" is a clearer designation.[4] The allergic agent may be a drug or the condition may result from infection of bacterial or viral origin.

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ITP is generally divided into two large categories, acute and chronic. Each form has distinct clinical and laboratory features. The etiology, pathogenesis and treatment of the acute form differ from those of the chronic form; therefore, we will discuss each of them separately.

Acute ITP

The acute form of ITP occurs most commonly in children, and frequently an infection of the respiratory tract precedes it. Bleeding from the mucous membranes is common, and epistaxis is an early sign. Petechiae and ecchy-

moses involve the mucous membranes and the skin. Active children normally demonstrate small ecchymoses of the extremities, usually pretibial, but patients with ITP have scattered lesions on the trunk and face as well. Often the child with ITP does not appear acutely ill or have significant physical findings. Occasionally a more serious gastrointestinal or an intracranial hemorrhage may complicate the picture.

It is extremely important to differentiate ITP from myelotoxic states and the leukemias as well as the secondary hypersplenism of congestive splenomegaly, lymphoma, tuberculosis and any other conditions leading secondarily to splenic enlargement. This can be accomplished by appropriate history taking, clinical examination and studies of peripheral blood and bone marrow.

In recent years, bone marrow studies have yielded a characteristic although not absolutely specific pattern for ITP. Paradoxically the number of megakaryocytes is normal or increased;[5] however, platelet production is greatly diminished.[6] Morphologic changes in the megakaryocytes in ITP consist of intense cytoplasmic vacuolation and loss of azurophile granulation; the importance of these changes has been underlined by their demonstration in control subjects following the administration of plasma from a patient with high-titer platelet agglutinin.[7] Thus the differential count of the megakaryocytic system is an integral feature of the bone marrow report in the study of a patient who has a low platelet count or purpura.

One must also consider the diagnosis of systemic lupus erythematosus in all cases in which thrombopenia is the major finding. The L. E. cell test is useful in this respect.

The initial management of ITP usually requires hospitalization. Bed rest and avoidance of exertion and straining are recommended. All potential bone marrow-depressing medications are avoided.

Adrenocorticotropin (ACTH), cortisone and related steroids are extremely useful in management of ITP. Within 24 hours of their administration there is a definite improvement in vascular resistance and in most instances bleeding ceases. These agents also appear to have a myelostimulatory action and aid in inhibiting the basic antigen-antibody reaction in the pathogenesis of the disease.

Adults are given ACTH intravenously in amounts equivalent to 1 unit per pound of body weight. Cortisone is administered orally, 2 mg. per pound of body weight. In addition they receive potassium supplements, 1 gm. three times a day, and a diet containing 1 gm. of salt. Subcutaneous and intramuscular injections are avoided because of the hemorrhagic status. Antibiotics, if needed, and analgesics (codeine) are administered by mouth. Chloral hydrate, 3.75 gr. twice during the day and 7.5 gr. at night, gives proper sedation.

In many cases of acute ITP a spontaneous remission occurs within two to four weeks. Therapy is indicated in an effort to shorten the course and counteract serious and sometimes fatal internal hemorrhages. Patients who demonstrate platelet antibodies reportedly respond most favorably to ACTH, cortisone and splenectomy.[8]

Five to seven days after institution of therapy an increase in the platelet count is regularly noted. The ACTH or cortisone is reduced gradually stepwise to levels of 15 to 20 units of ACTH or 50 to 75 mg. of cortisone. Dosage is maintained at this level for two to three weeks if the platelet response is favorable. A low salt diet and administration of potassium are indicated.

Occasionally a patient with acute ITP will not respond to ACTH or cortisone (figures 1 and 2) but will have a satisfactory result after splenectomy is performed. ACTH and cortisone have been extremely useful in preparing patients for splenectomy in spite of incomplete platelet response. These agents have reduced the morbidity and mortality due to excessive bleeding. At operation a careful search should be made for accessory spleens. Often they are found in the hilus of the spleen and less frequently in the omentum. They should not be confused with lymph nodes (figure 3).

Splenectomy is advised in all cases in which medical management with ACTH or cortisone produces an incomplete response and when relapse occurs after a course of therapy. In

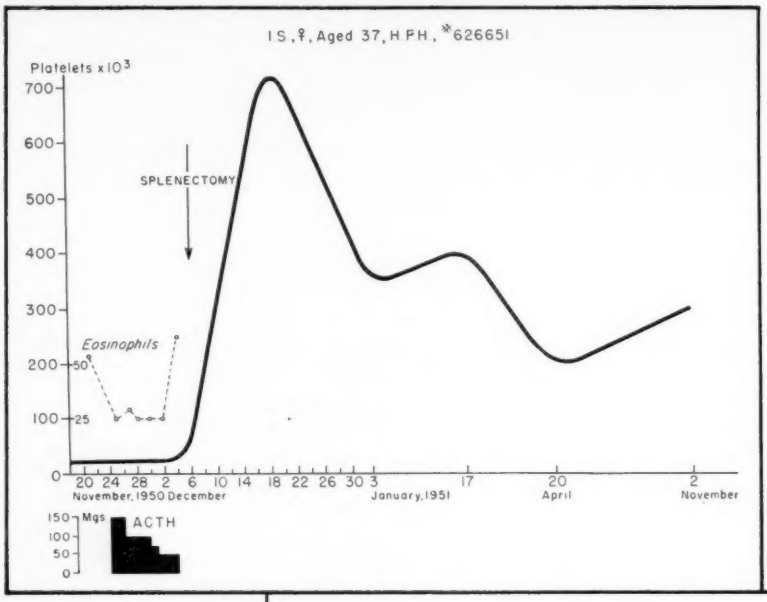

FIGURE 1. Acute idiopathic thrombopenic purpura with failure of platelet response to ACTH. This lack of apparent improvement with ACTH does not predict a poor result with splenectomy.

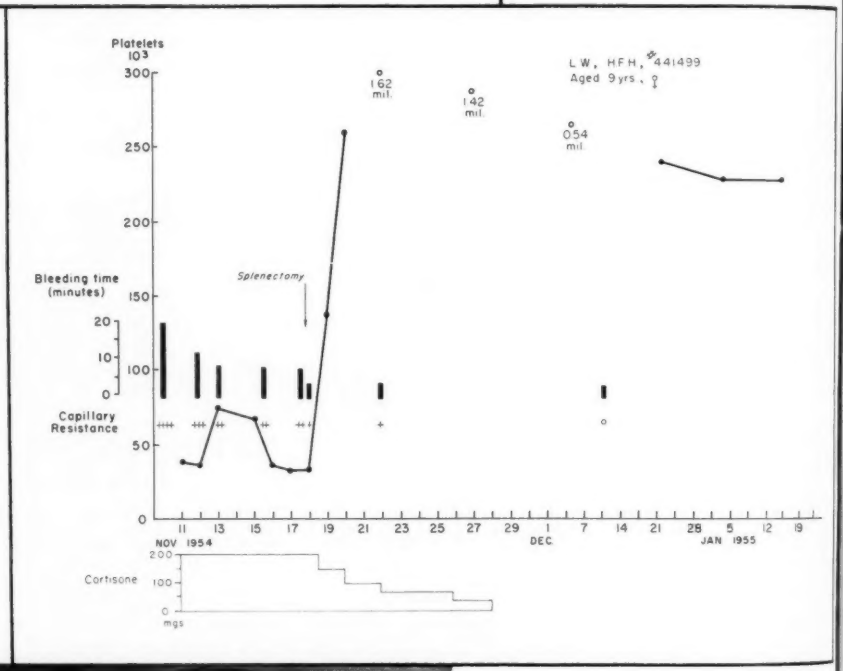

FIGURE 2. Acute idiopathic thrombopenic purpura. Minimal transient response in platelet production to cortisone therapy. Splenectomy was performed because of suspicion of intracranial bleeding. Note shortening of the bleeding time and increased capillary resistance following steroid therapy. Lack of adequate response to cortisone does not suggest that splenectomy will give a poor result. The repeated observation of this phenomenon suggests a separate method of action for each modality.

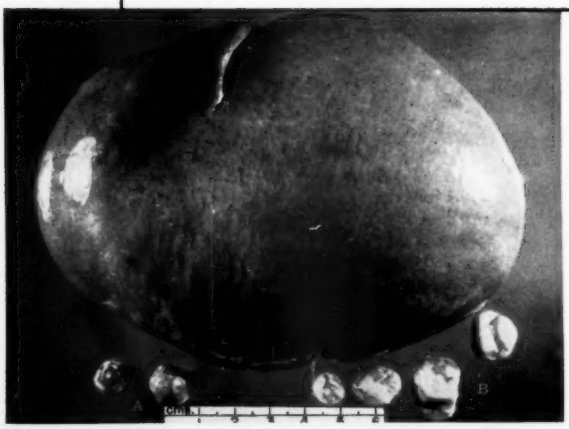

FIGURE 3. Surgical specimen, splenectomy in a case of chronic idiopathic thrombopenic purpura. Accessory spleens found in hilus and mesentery of bowel (A). These are not to be confused with frequently encountered enlarged abdominal lymph nodes (B).

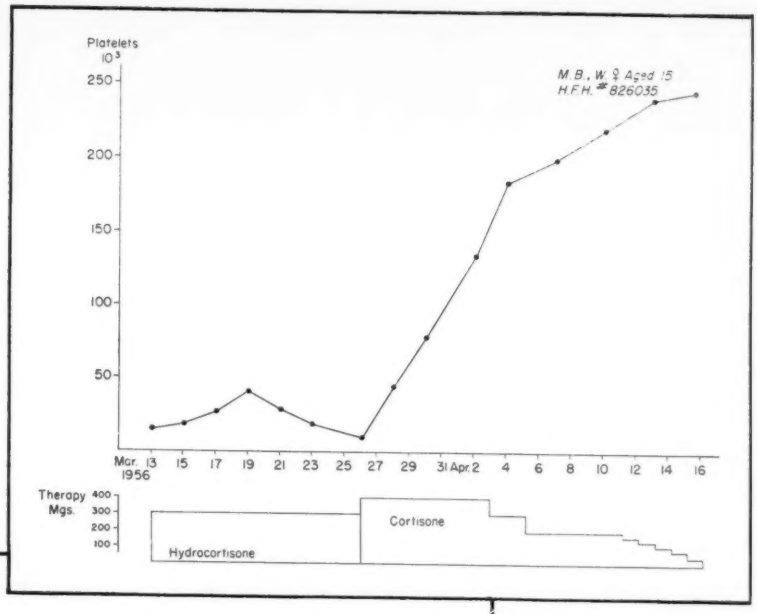

FIGURE 4. Acute idiopathic thrombopenic purpura. Minimal and fleeting improvement with hydrocortisone, followed by satisfactory remission with cortisone.

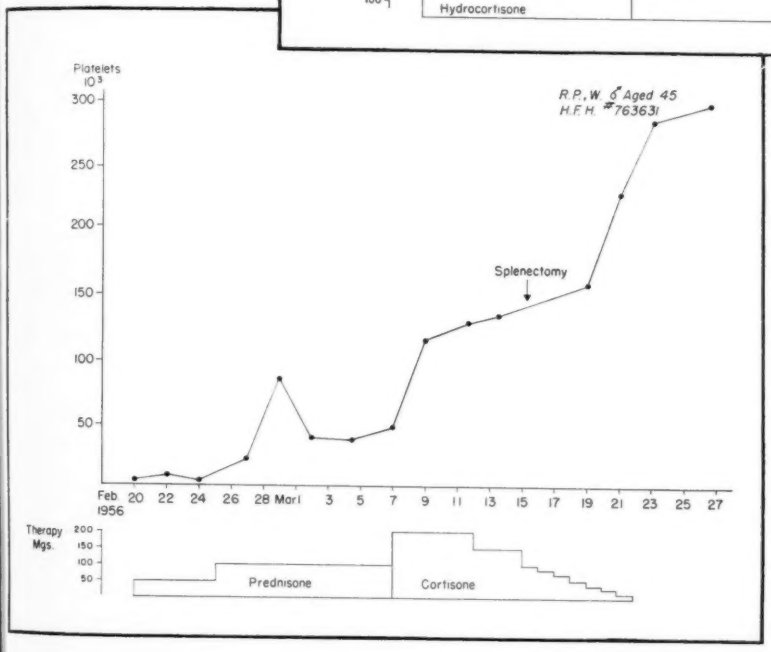

FIGURE 5. Acute idiopathic thrombopenic purpura. An incomplete transient response to prednisone, partial remission with cortisone, and finally cure by splenectomy.

children, medical management is tried for at least four to six weeks before splenectomy is advised.

Hydrocortisone and prednisone generally give less satisfactory results than the parent compound cortisone (figures 4 and 5).

In thrombopenia caused by sensitization to certain drugs, hormone therapy is of value. Withdrawal of the offending agent would result in remission, but added safety is afforded by use of cortisone to arrest hemorrhagic manifestations (figure 6). Often the offending drug or chemical is not obvious. Administration of a "diagnostic test dose" is not recommended because a severe positive reaction may be disastrous.

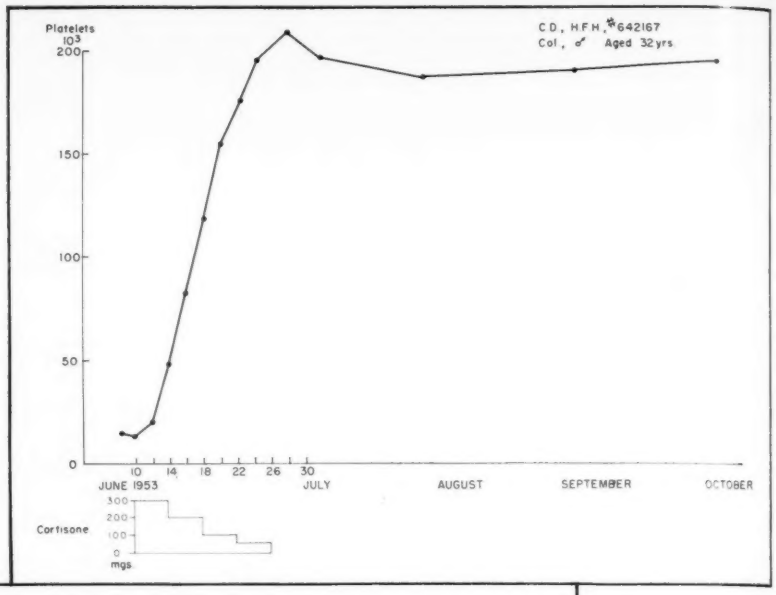

FIGURE 6. Secondary thrombopenic purpura produced by administration of quinidine. Withdrawal of the drug would result in remission, but administration of a steroid is of value in controlling mucous membrane bleeding and may help prevent serious intracranial hemorrhage.

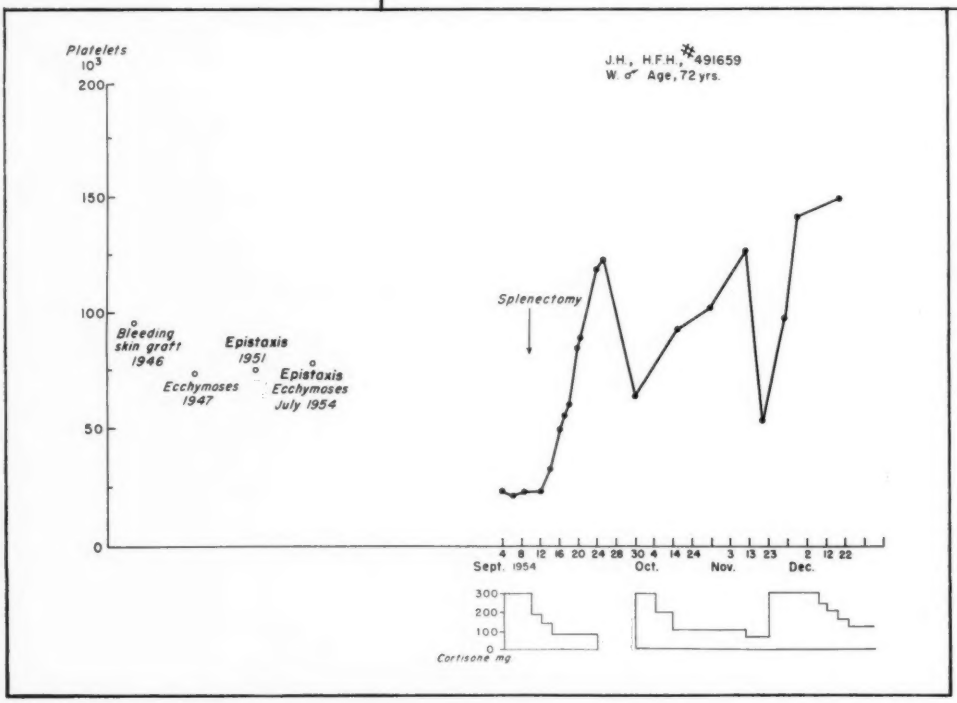

FIGURE 7. Chronic idiopathic thrombopenic purpura. History suggested a bleeding disorder of several years' duration. While initial cortisone therapy did not strikingly increase the platelet count, it did minimize bleeding at the time of splenectomy. Subsequent relapses were easily controlled by the administration of cortisone.

Chronic ITP

The chronic form of ITP usually affects adults, and often a clear history of an initial acute phase is lacking. Frequently the hemorrhagic symptoms first appear following minor surgery such as dental extractions or are related to prolonged menses or recurrent epistaxis. The platelet count usually is not as strikingly reduced in the chronic form as it is in acute ITP, being in the range of 40,000 to 80,000 per cubic millimeter.

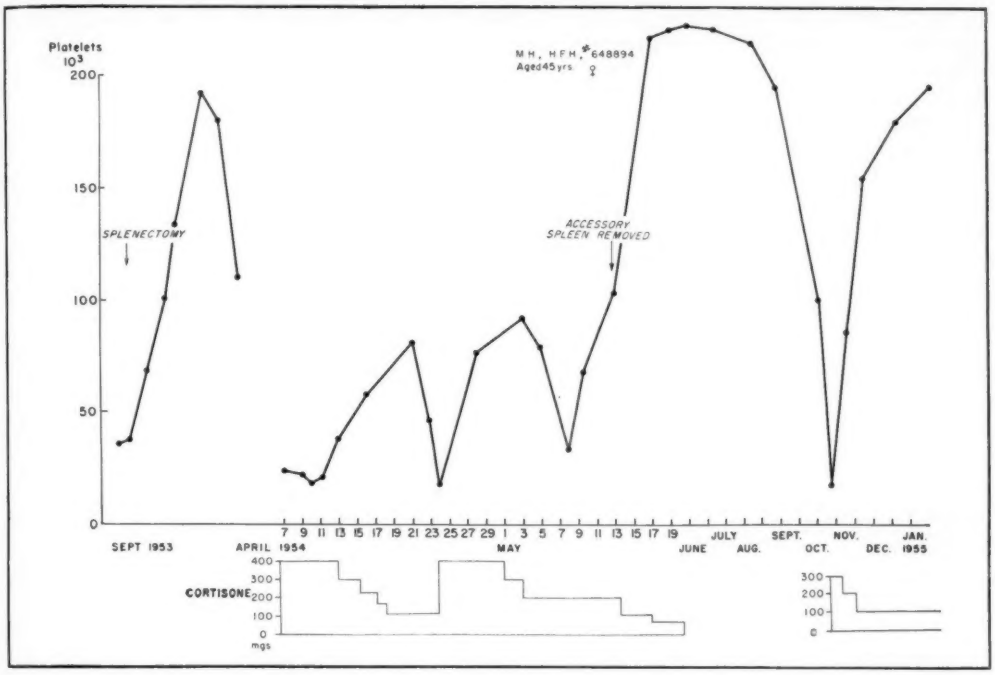

FIGURE 8. Chronic idiopathic thrombopenic purpura. Splenectomy performed elsewhere produced a transient remission. Subsequent relapses were favorably influenced by cortisone therapy. Removal of accessory spleen gave a temporary remission, but steroids were again needed at a later date. This patient had a mild photosensitive dermatitis and on rare occasions an L.E. cell was found, suggesting the diagnosis of systemic lupus erythematosus.

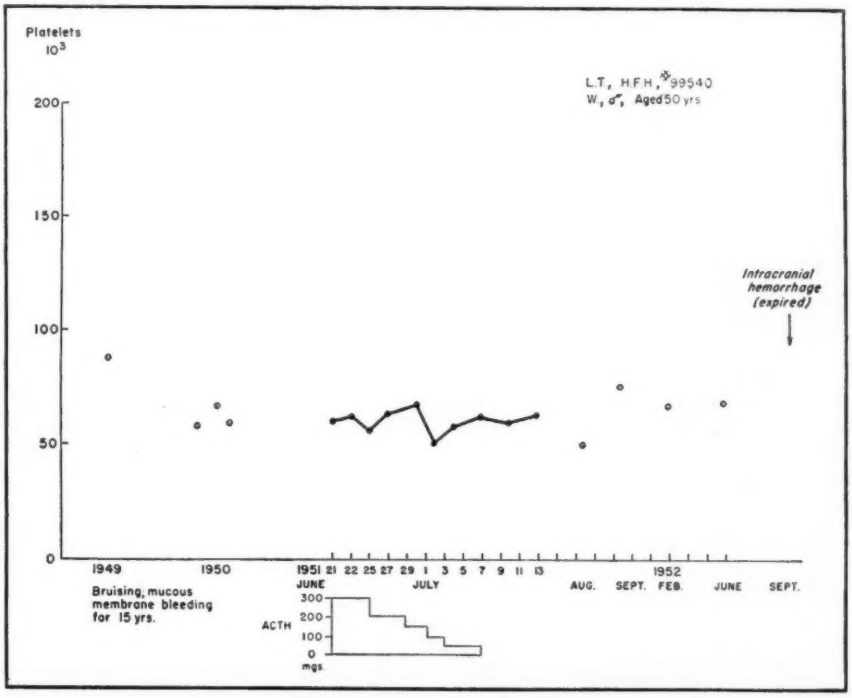

FIGURE 9. Chronic idiopathic thrombopenic purpura. Patient was referred to us, and did not respond to cortisone therapy. Splenectomy was advised but refused. This represents the only fatal case in our series.

As in the acute form, a careful survey is mandatory to exclude primary organic disease. Chronic ITP of many years' duration is relatively rare compared with the acute form.

Splenectomy is advised in chronic ITP, and the patient is first prepared with ACTH or cortisone. A platelet response is regularly noted following use of these agents, and operation is performed when levels of 80,000 to 100,000 per cubic millimeter are reached (figure 7). Occasionally a patient will respond incompletely or only transiently to splenectomy. One can control these cases indefinitely by administering cortisone (figure 8).

Discussion

In the past few years the number of splenectomies which have been performed in cases of idiopathic thrombopenic purpura have been greatly reduced. Indeed it appears that the incidence of the acute form of the disease is diminishing. We may speculate that the widespread use of antibiotics and chemotherapeutic agents for the control of infection has reduced the immunologic response causative in the pathogenesis of ITP. In addition the usefulness of ACTH and cortisone in medical management of these patients has given the physician added confidence when awaiting a remission.

Since 1951 we have treated 62 patients with idiopathic thrombopenic purpura with ACTH and cortisone, with and without splenectomy. Only one death occurred in this group. In this case the patient refused splenectomy after cortisone therapy was unsuccessful (figure 9). ACTH or cortisone was given to 42 patients, and 20 of these had an incomplete response and underwent splenectomy. In two cases* the disease remained chronic but symptomatic control was obtained by long-term cortisone treatment. There were no deaths among the 20 patients in whom splenectomy was performed, and there was no significant morbidity.

*High platelet agglutinins were demonstrated in the serum of these two patients.

Summary

It is believed that idiopathic thrombopenia has an immunoallergic basis. There are two forms of the disease, acute and chronic, and the clinical picture and laboratory findings are distinct. Most patients with acute ITP can be successfully treated with ACTH or cortisone. Those with acute ITP in whom there is an incomplete response to steroid therapy and those with the chronic form of ITP are subjected to splenectomy. The patients are prepared for operation with ACTH or cortisone.

Successful treatment depends on accurate diagnosis to exclude other forms of thrombopenic purpura. Careful medical observation and vigorous ACTH and cortisone therapy have reduced the need for splenectomy.

A series of 62 adequately treated cases of ITP are cited in which there was only one death, that of a patient who refused splenectomy after cortisone failed to produce an adequate response. In two cases there was only temporary improvement with combined steroid therapy and splenectomy, but symptomatic control was achieved by long-term cortisone therapy. It appears that cortisone gives more satisfactory results than hydrocortisone or prednisone.

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The Process of Aging Has Emotional Problems

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SINCE 1940 the number of persons 65 years of age and older in the United States has increased by nearly 50 per cent and the total is now 13,500,000. In the state of New York alone the 65-and-over group increased 39.3 per cent between 1940 and 1950 compared with an increase of 10 per cent in entire population. These figures point to the need for an active program aimed at alleviating the many problems involved in the aging process.

We have begun to think of aged persons in terms of who they are, where they live, what they want out of life, and their need for recreation, economic security and health. Further, we have come to recognize that aging is a gradual process characteristic of the adult life span, that individual rate differences are great, that people do not grow old emotionally, intellectually and physiologically at the same rate, and that chronologic age is not the most accurate index of any aspect of aging.

Most important, from the standpoint of preventive medicine it would appear that the most constructive efforts to promote welfare in old age must begin prior to old age. The burden of this problem falls primarily on the general practitioner, for does he not occupy the leading role in the case of disabled aged persons?

The general practitioner is trained to focus his attention on physical health and relief of suffering and impairment resulting from organic disease, and therefore the emotional elements may not seem too significant. The psychiatrist, on the other hand, in an attempt to understand behavior on the basis of the integrated whole, studies the total personality with emphasis on the emotions, intellect and environmental factors.

Many years ago the late Frankwood E. Williams, formerly director of the National Committee for Mental Hygiene, worked out a definition for mental hygiene as follows: "Mental

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hygiene is the art of application of knowledge derived from certain basic sciences to the maintenance of individual mental health. Mental health should not be interpreted too narrowly as merely freedom from disease but broadly in the sense of behavior and the ability to attain and maintain satisfactory human relationships. This ability depends upon the potentialities of the individual for physical, intellectual and emotional growth on the one hand, and opportunities for growth on the other."

As a psychiatrist, my interest is chiefly in the emotional aspects, but as a physician I cannot ignore the fact that every patient has an intellect and a physical component as well. The eclectic school of psychiatry, whose greatest exponent was the late Adolph Meyer, has always stressed man as an integrated being with all components of his personality, under normal conditions, beautifully co-ordinated and wonderfully synchronized—in other words, operating as an integrated whole.

Too often the general practitioner sees in his patient only the organic man and consequently treats only the diseased organ or organs, forgetting entirely the total personality and overlooking the environmental factors involved. For this reason I should like to point out the factors concerned in the aging process but perhaps, because of my specialty, placing emphasis on emotional problems.

As to the physical disorders seen in older patients—and they are many—we should concern ourselves with diagnosis, definitive care and, more important still, rehabilitation. Recognizing that deterioration—skeletal, muscular, chemical and mental—is remarkably more rapid in the aging patient than in the younger one, early ambulation of hospitalized persons is definitely indicated.

Our approach must be dynamic, not static, and the attitude of the hospital personnel must be hopeful and positive to prevent institutional apathy. Frequently a form of group therapy helps to stimulate indifferent patients to enter enthusiastically into a rehabilitation program. Every effort should be made to achieve some degree of restoration to physical independence within the capabilities of the individual, thus raising his morale and building up his ego. The same applies to home care, where the physician may enlist the aid of the family.

Having rendered the patient physically independent, insofar as possible, efforts should be directed at attaining social and possibly economic independence. Recreational activities require attention at this point.

Some eight years ago the Onondaga Health Association, of which I was president, surveyed the needs of the older citizens of the city of Syracuse, New York. They found that many of the prerequisites of everyday living which are essential to social, personal and economic security were denied this forgotten group. The Salvation Army, which caters to a large segment of our older population, was instrumental in organizing a Golden Age Club, and as a psychiatrist I was asked to serve on the advisory board.

The project began modestly. The "club room," a part of the rather antiquated Citadel, was a shabby meeting hall with none of the appointments that make for comfort and beauty, and only one member of the Salvation Army staff could be spared on a half-time basis. On October 28, 1949, a small group of oldsters were invited to join Golden Age Club No. 1. Only 16 attended the first meeting, but within a few months more than 60 happy senior citizens were attending the regular Friday afternoon sessions. A planned program of games and light entertainment followed by refreshments and a social hour constituted the activities during the early days of the club.

The need for occupational therapy was soon apparent, and early in 1950 a workshop was opened, affording a place where members could learn new skills and be happily occupied five days a week. A woodworking shop was set up for the men, and the women busied themselves with glass and figurine painting, weaving, rush work, leather and needlecrafts.

A detailed account of the rapid expansion of the program is beyond the scope of this article, but mention should be made of the summer camp, the extension services for persons confined to their homes, the 25 convalescent homes in Syracuse, and the "friendly visitors" program.

The Junior League of Syracuse became interested in the problem, and through the Council of Social Agencies it offered to underwrite, both financially and with volunteer service, a Council of the Aging for one year. I was asked to serve as the first chairman and accepted gladly, for two reasons: (1) A very dynamic and able executive secretary was available to carry forward the program, and (2) my interest in the aged and their problems had been deeply aroused through my association with the Salvation Army's Golden Age program.

On June 22, 1950, we called a meeting of a small group of persons whom we knew were interested in the project, representing the Junior League, the Council of Social Agencies, and other community groups, and the Council on the Aging was formally launched.

Article II of our bylaws outlined the aims and purpose of the organization as follows:

1. To study existing conditions and problems surrounding the aging population in the community.
2. To stimulate other agencies to reshape their programs and services where necessary, in order to prevent and lessen problems of the aging.
3. To promote new services or programs as needed.
4. To educate the community and create a climate of opinion which will facilitate the achievement of the goals outlined above.

Five comparatively small *working* committees were appointed: Medical and Nursing Care, Education and Recreation, Economic Security, Institutional Care, and Housing and Research.

The first year of activities consisted largely of exploration. The second year was one of adventure and experimenting. We were amazed at the magnificent and wholehearted participation of many citizens and organizations. The high light of the second year was our selection by the Ford Foundation as the basis of its March 16 "People Act" broadcast. This brought us nationwide recognition and spurred us on to further accomplishments.

Perhaps I have stressed organization unduly rather than dwelling on "emotional aspects" of aging, but in view of the hundreds of requests we have received since the "People Act" broadcast I do not feel it is amiss to give some hint as to how "great oaks from little acorns grow."

In our contacts with our "senior citizens," certain emotional needs have been evident. In approaching this phase of the problem, we may put forth the question, What are the thoughts and feelings of the aging?

It would appear that in the involutional phase of the life cycle the ordinarily adequate adjustment between the instinctive forces of self-preservation and race preservation breaks down and a new psychologic attitude is required. The self-preservative drive becomes predominant, resulting in an overawareness of self and a lack of concern for others which occasions a most serious problem of adjustment. The required change of philosophy may fail and apprehension and depression follow. Frequently one encounters a picture of neuroticism because the senior citizen often distorts reality and exaggerates his limitations. His whole outlook becomes pervaded by a cynical attitude because external stimuli lose their zest and he derives no pleasure from former anticipations.

The aging individual tends to isolate himself because diminished sensory acuity, especially of sight and hearing, interferes with his social acceptability and ability to maintain effective communication with the environment. This particular problem may be aptly termed "social disarticulation," and often leads to misinterpretations and suspicions which if uncorrected become distorted and result in increasing anxiety, fear and discouragement.

There are so many physical changes incidental to advancing age which constitute a real threat to the oldster, but the manner in which these changes are accepted is the important consideration. Hence, every effort must be made to revise the feelings of inadequacy with occupational therapy and psychotherapy.

Let us for a moment consider the effect of environment on the emotional response of the senior citizens. Perhaps enforced retirement constitutes the most devastating blow to the ego. Arbitrary retirement at age 60 or 65 is most unfortunate when a person feels fit and

has the capacity and desire to work. Definite and constructive plans are needed which preferably would be put in operation long before retirement is imminent in order to prepare the aged for retirement. Feelings of uselessness produce tensions, irritability and anxiety.

Some industries provide special orientation courses for five years preceding the date of retirement, and this is indeed a worthwhile mental hygiene measure and should be employed more widely.

Consideration should also be given to other factors such as the attitude of friends and family, financial insecurity, and so on.

Briefly, after six years' experience our Council on the Aging believes that the outstanding needs of the senior citizens are an opportunity to be useful and creatively productive, a chance to be active, a feeling of being loved and wanted, financial security, and, above all, the feeling that they are free human beings. Our various committees have worked and are still working to supply these needs. But there are certain adjustments which are the primary responsibility of the elderly person himself. These include acceptance of declining physical capacity, learning to live on reduced income and possibly accepting a lower social status, effective utilization of increased leisure, and the development of a basic philosophy toward later life. We can help in these adjustments through a greater understanding of their emotional problems and through active participation in dynamic programs aimed at physical rehabilitation, social and economic independence, and education of the public.

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CYSTIC FIBROSIS

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CYSTIC fibrosis is a little-recognized disease of major importance found mostly in infancy and childhood (Am. J. Med. 21:406, 1956). The incidence is estimated at 1.7 per thousand births. Duration of survival depends mainly on the inherent severity of the pulmonary component and the quality of medical management.

Supported in part by the National Cystic Fibrosis Research Foundation, the Cystic Fibrosis Association (Nebraska), and the A.M.A. Council on Pharmacy and Chemistry.

Adapted from an exhibit at the 1956 Clinical Session of the American Medical Association at Seattle.

Clinical Manifestations

Meconium ileus—Intestinal obstruction in the newborn period in 10 per cent.

Bronchitis, pneumonia, bronchiectasis—Cough, rales, dyspnea, cyanosis, clubbing.

Chronic diarrhea, malnutrition—Soft, foul, bulky stools; protuberant abdomen; wasted musculature; large appetite.

Sweat defect—Vomiting and shock in hot weather due to excessive loss of salt in sweat.

Pulmonary Changes

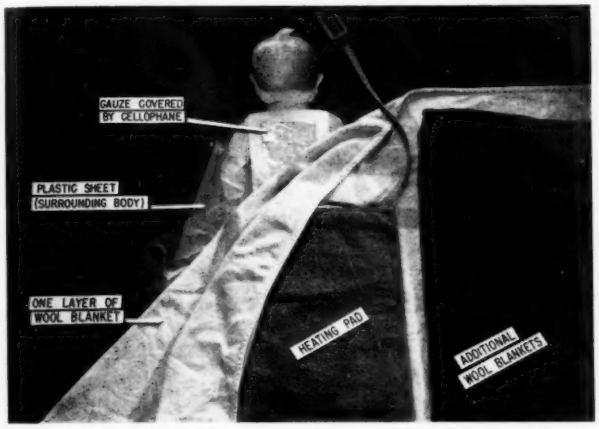
In cases of cystic fibrosis with advanced pulmonary changes, x-rays show linear or patchy densities radiating from the hili.

Diagnostic Tests

Simple tests for fat and trypsin in stool can partially confirm diagnosis of cystic fibrosis. Fat is observed microscopically with Sudan III stain. X-ray film is used in a test for trypsin. When a 1:10 dilution of soft, normal infant stool is left on x-ray film for 30 to 90 minutes and then rinsed off, a translucent area is found.

These tests are subject to various confusing factors such as low fat diet, other steatorrheas, mineral oil, stale stool, and proteolytic bacteria. Rarely are both tests misleading at the same time, however.

Sweat Test
Principal Test for Cystic Fibrosis



Equipment for performance of the sweat test.

Centrifuge tube with wire platform.*

Sponge back with distilled water and wipe dry with clean gauze.
Apply strips of opened 2 by 2 in. gauze (handle gauze only with forceps).
Cover area of gauze with cellophane (tightly sealed at edges with adhesive tape).
Wrap baby in plastic sheet and place supine on several thicknesses of wool blanket.
Place one layer of blanket over baby.
Place one or two 60 W electric heating pads on the single layer of blanket.
Wrap baby with two or three additional wool blankets.
Let heating proceed until abundant perspiration appears on face.
Place gauze pads in centrifuge tube equipped with wire platform (one 15 ml. tube holds two 2 by 2 in. pads).*
Centrifuge, with tube covered by cellophane held by rubber band.
Titrate chloride by routine method for blood filtrate (J. Biol. Chem. 140:879, 1941); deproteinization is not necessary, and 0.2 ml. is sufficient.

This procedure for the sweat test avoids the necessity for any special plastic bag. Heating is vigorous but reproducible, and abundant sweat is obtained in 20 to 40 minutes without serious discomfort.

The wire platform for the centrifuge tube is a small roll of ¼ in. mesh.* Free undiluted sweat is obtained from the gauze by centrifuging. This feature of the test was developed for the purpose of providing undiluted sweat for dermination of special constituents. Volumetric portions of sweat are taken, avoiding weighings of gauze. The chloride or sodium, or both, can then be determined by routine blood methods.

This technic of sweat collection has become routine at the University of Nebraska Hospital and the Children's Memorial Hospital in Omaha, and has been turned over satisfactorily to a physiotherapy technician or pediatric nurse. The sweat is delivered to the routine clinical laboratory for analysis.

*Recently, plastic golf tees have been found more satisfactory than wire rolls.

Chamber to hold disk of filter paper for collection of sweat from small area.

Filter Paper Technic

Another technic of sweat collection utilizes an aluminum ring 20 mm. in diameter with a close-fitting cover enclosing a disk of filter paper (J. Exper. Med. 97:429, 1953). The local area of skin is stimulated by an injection of acetylcholine placed intradermally by the subcutaneous route. The quantity of sweat is found by weighing the filter paper before and after sweat collection. This technic sometimes is more convenient for outpatient adults than generalized thermal sweating. Titration of the chloride is done with a capillary buret.

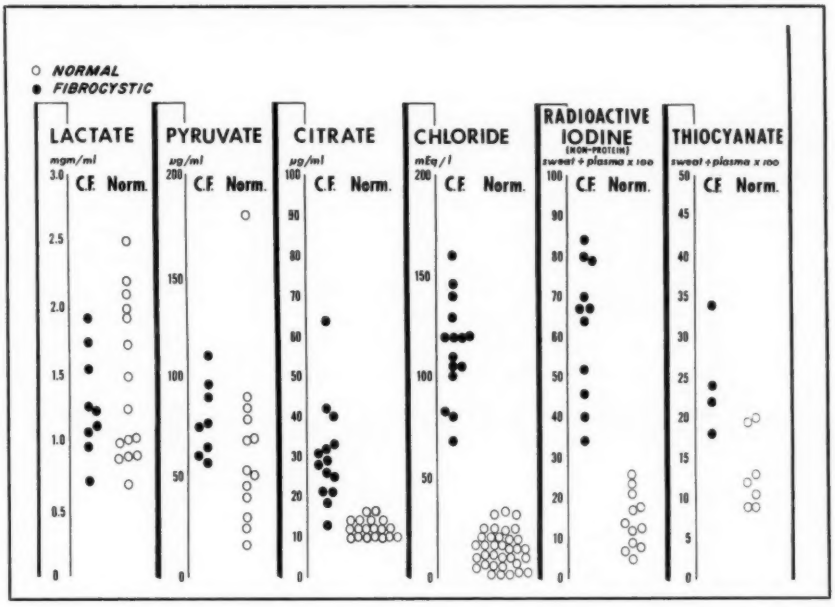
The Sweat Abnormality in Cystic Fibrosis

The organic acid intermediates of carbohydrate metabolism are of interest in a search for the basic disorder of the various exocrine glands in cystic fibrosis. There does not seem to be a significant deviation from normal with respect to lactic and pyruvic acids. "Citric acid," however, seems to be elevated in cystic fibrosis. "Citric acid" was determined by the method of Krog (Acta physiol. Scandinav. 9:68, 1945). This method has proved not to be specific for citric acid but to include other related compounds capable of being degraded to acetone. The exact compound responsible for the elevation of apparent citric acid remains to be identified but the disturbance observed offers a possible clue to a disturbance in the citric acid cycle of aerobic carbohydrate metabolism.

The wide difference in chloride levels between normal persons and patients with cystic fibrosis illustrates the known defect in sodium chloride content of sweat in this disease.

Radioiodine, another halogen, was also studied. A dose of Lugol's solution was first given to saturate and protect the thyroid. Radioiodine was then given in a dosage of approximately 2 microcuries per kilogram of body weight, up to a maximum of 30 microcuries. The radioactivity of the sweat was then determined and related to the nonprotein iodine radioactivity of the serum. The elevated levels of radioiodine in sweat are similar to those of chloride.

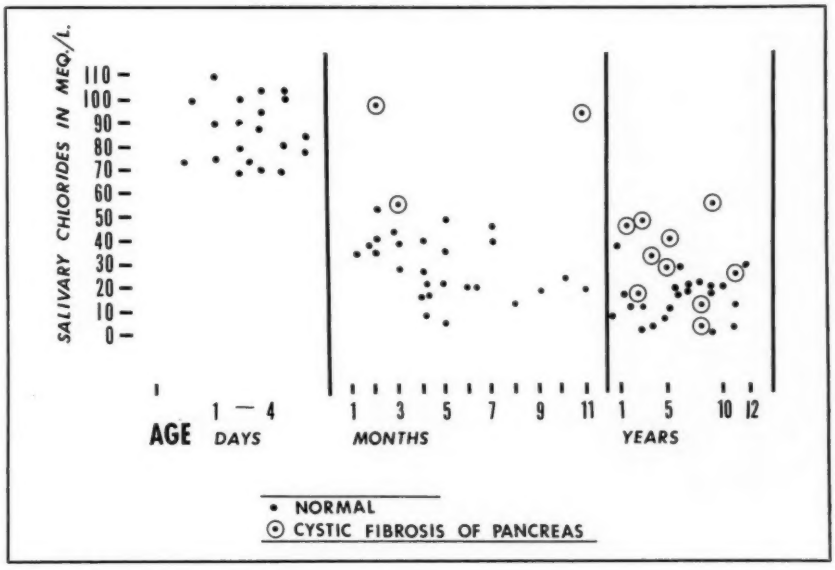
A similar relationship seems to exist with respect to thiocyanate, which has been considered to act physiologically as a halide in other conditions also.



Preliminary results of current research on constituents of the sweat in cystic fibrosis (done in collaboration with V. M. Wilder, S. McAndrews, J. S. Brodkey, A. T. Tuma and R. H. Hutchings, and sponsored by the National Cystic Fibrosis Research Foundation).

Salivary Chloride

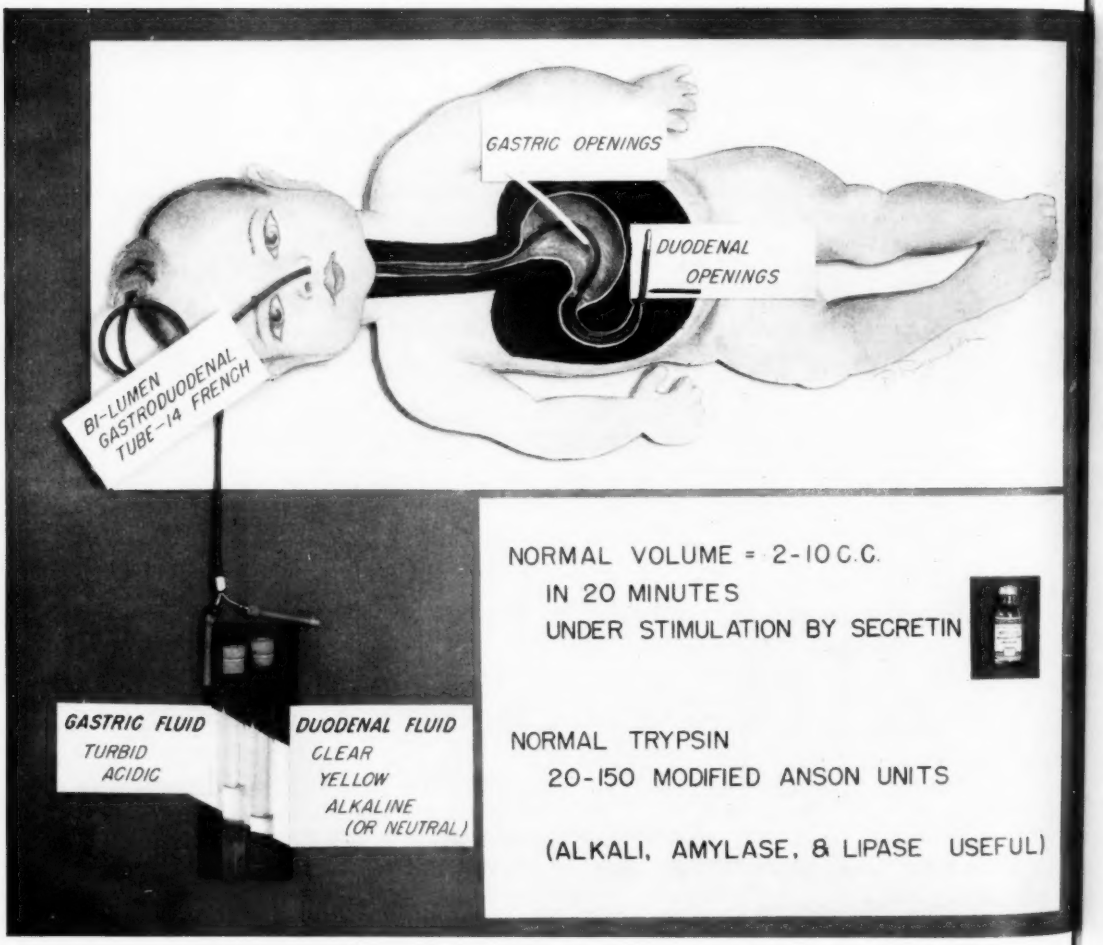
A tendency for chloride to be elevated in cystic fibrosis is apparent. In the newborn period saliva was scanty, and chloride in normal infants was elevated in comparison with values found at later ages.



Chloride in parotid saliva in cystic fibrosis. (B. B. Kumar.)

Pancreatic Deficiency

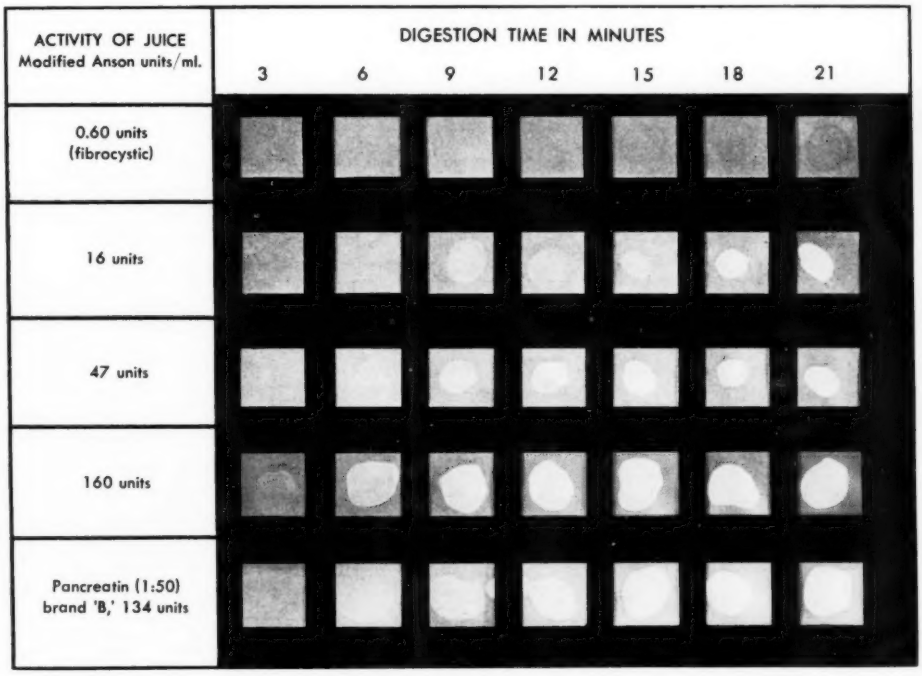
For drainage of duodenal fluid, a double-lumen gastroduodenal tube is used. This is essentially a small Einhorn tube. Such a tube is easily made from a No. 14 Fr. Miller-Abbott tube by cutting off the end, making some perforations near the end of one lumen and 15 cm. higher on the other, and attaching a metal tip. The duodenal fluid is clear and yellow and alkaline or neutral in pH. Gastric fluid is turbid, colorless and acid. Use of the double-lumen tube minimizes contamination of the pancreatic specimen by gastric contents. It also is convenient in that it provides evidence of correct positioning of the tube without x-ray. Different fluids come simultaneously and separately from the gastric and duodenal lumina.



Duodenal drainage for diagnosis of pancreatic deficiency.

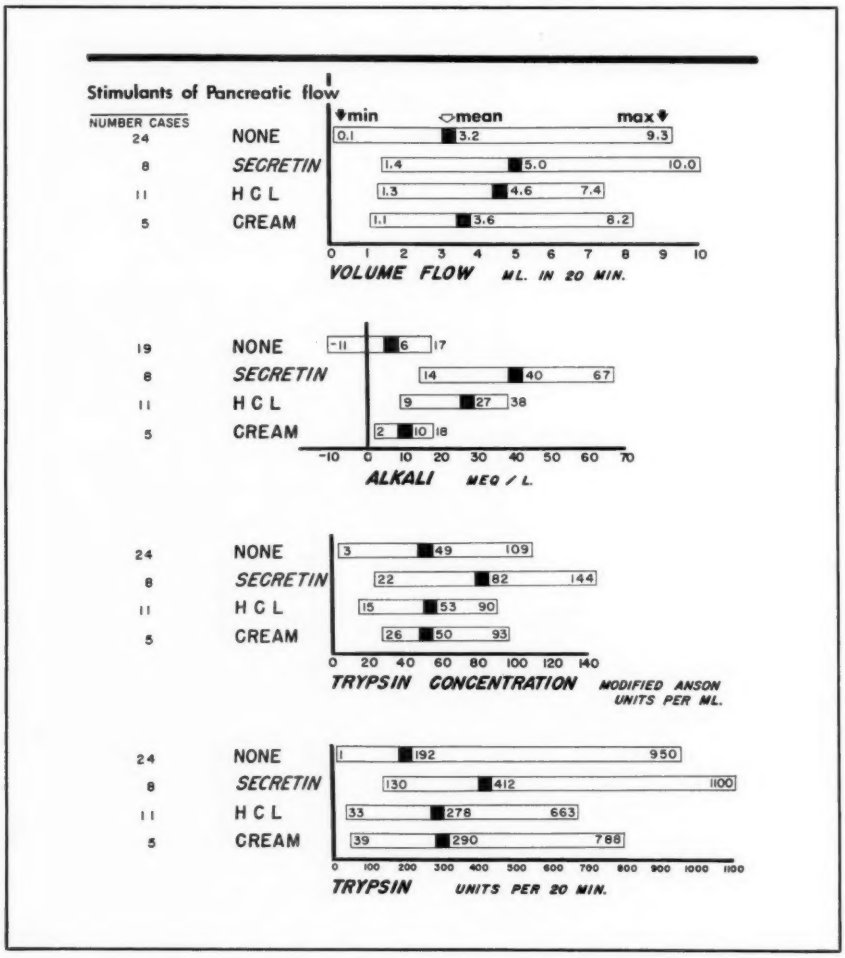
For a rough evaluation of the enzyme content of pancreatic juice, the duodenal aspirate may be placed, *undiluted*, on pieces of x-ray film and left *at room temperature* for different periods. The juice is then washed off the film. Tryptic digestion of gelatin is indicated by translucent areas. Thus, in cystic fibrosis, with 0.6 modified Anson unit of trypsin per milliliter of juice, there was no translucency even at 21 minutes. With 16 units there was slight clearing at nine minutes and strong clearing was apparent at 18 minutes. With 160 units of trypsin some clearing was noted at three minutes and strong clearing at six minutes. For comparison, the effect of 1:50 dilution of pancreatin is shown.

This simple technic is available to any physician and is useful in indicating pancreatic function. Pancreatin can be used to check the suitability of the x-ray film, or the film can be used to check the potency of a pancreatin preparation.



Duodenal aspirate (undiluted) is used to digest the emulsion of undeveloped x-ray film. The degree of digestion roughly indicates the activity of trypsin.

Twenty-four studies were done on the same normal infant, with and without stimulation to pancreatic flow. Dosage of secretin was 40 clinical units (2 ml.) per square meter of body surface. Hydrochloric acid was given by duodenal tube in a dosage of 25 ml. N/20 per square meter of body surface. Cream was given, also through the duodenal tube, in a dosage of 35 ml. per square meter of body surface. The secretin produced a greater response than hydrochloric acid or cream. The advantage of secretin was particularly notable with respect to alkali production. In a few unstimulated samples the volume, alkali and enzyme would have given a false impression of pancreatic deficiency.



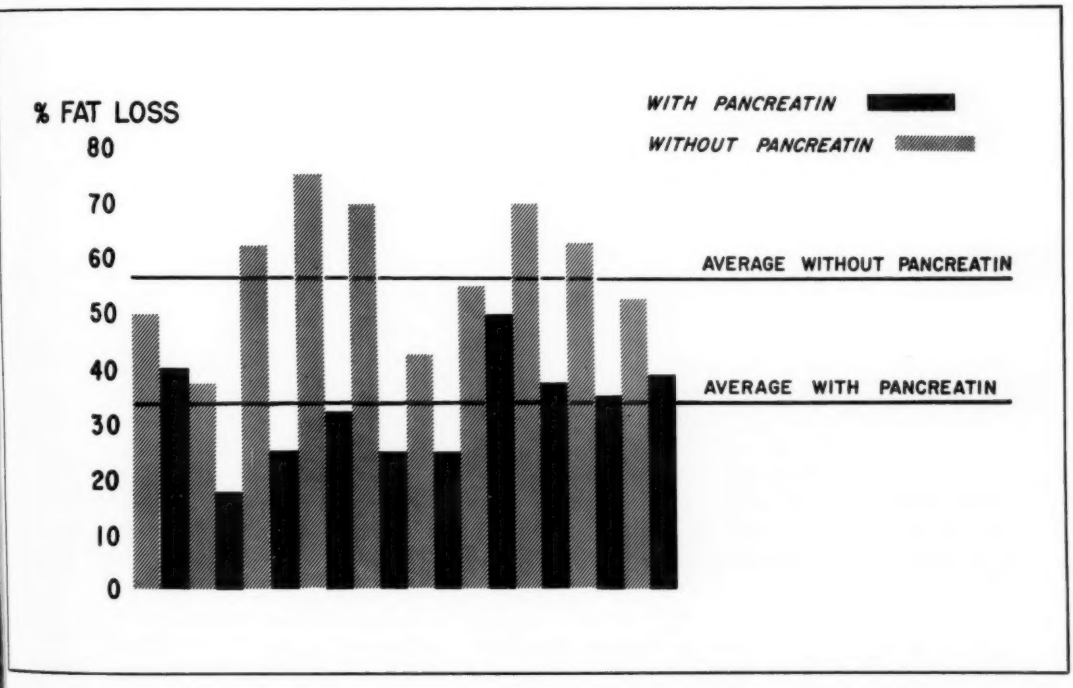
Reproducibility of duodenal drainage. Summary of 24 duodenal drainages in one normal nine month old infant, illustrating the influence of different methods of stimulation of pancreatic flow.

Treatment

Treatment of cystic fibrosis is nutritional, antibiotic and mucolytic.

Effect of Pancreatin on Fat Utilization

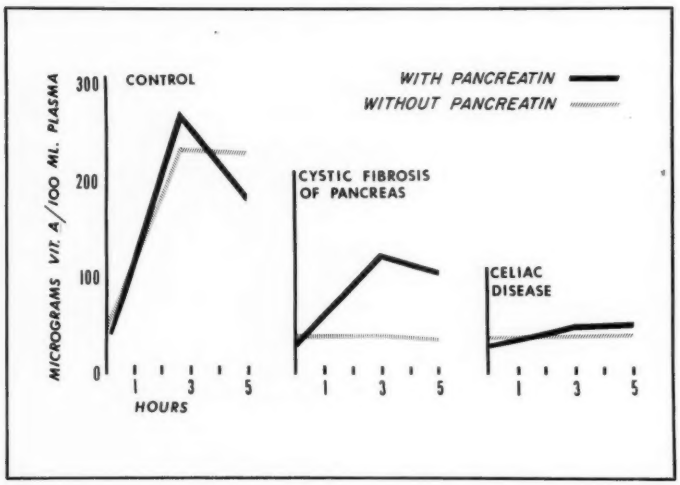
The simplified technic used to study the effect of pancreatin proved satisfactory on a routine pediatric ward. The diapers were lined with plastic to facilitate stool collection. The start of each period was marked with carmine placed in the formula. For analysis the total wet stool was mixed and weighed, and wet aliquots were saponified, acidified and extracted with petroleum ether. The fatty acids were titrated with isobutyl alcoholic potassium hydroxide in aliquots of the petroleum ether extract (J. Biol. Chem. 177:347, 1949). This study demonstrates the lipolytic effect of pancreatin.



Effect of pancreatin on fat utilization in 20 consecutive three day fat-balance studies in an infant with pancreatic exocrine deficiency (Am. J. Dis. Child. 91:606, 1956). Alternate periods were with and without pancreatin (viokase powder). Pancreatin dosage was 1 gm. with each feeding, five times daily. Feedings were whole milk. Balance periods were marked with carmine in the first feeding. Stools were collected with plastic diaper liners (SARAN WRAP®). Fat determinations were made on wet stool. (B. B. Kumar.)

Effect of Pancreatin on Plasma Vitamin A Curves

A related study showed the vitamin A absorption curve in cystic fibrosis and the effect of pancreatin to correct the flat curve in cystic fibrosis but not in celiac disease.



Effect of pancreatin on plasma vitamin A curves. Average curves of 15 control subjects, 32 cases of cystic fibrosis, and 10 cases of celiac disease.

Pulmonary Component

Treatment of the pulmonary component of cystic fibrosis involves the whole array of available antibiotics. The most common bacteria are staphylococci and *Pseudomonas*. Organisms resistant to common antibiotics appear. Sensitivity tests assist in choosing effective antibiotics. At times, favorable results have been obtained by aerosol use of neomycin and bacitracin (Antibiotic Med. 2:332, 1956). Toxic drugs can thus be used in a topical application by aerosol. Aerosol therapy is given by mask and nebulizer, four treatments per day in the home. An electric pump is usually used for pressure.

Aerosols are also used for possible mucolytic effect in intermittent treatment over long periods in the home. Clear evidence of benefit from "mucolytic" aerosols so used is not yet available but, except for antibiotics, the main hope of prophylaxis of the pulmonary component of cystic fibrosis seems to lie in further development of effective mucolytic agents and technics.

This exhibit is the first of a series of special presentations on "critical diseases"—conditions for which no definitive treatment has as yet been determined. See the editorial on page 546 relating to this special series.

Theory and Use of Antibiotic Combinations

PART 2: CLINICAL ASPECTS

The following abstracts were prepared from papers presented at the Brook Lodge Invitational Symposium, held at Kalamazoo, Michigan, and sponsored by The Upjohn Company. Devoted to a discussion of the theory and use of antibiotic combinations, these abstracts are the second in a two part series representing the laboratory and the clinical aspects of the subject. Part 1 appeared in the October issue of POSTGRADUATE MEDICINE.

Combinations of Antibacterial Drugs in Urinary Tract Infections

EDWARD H. KASS*

INFECTIONS of the urinary tract are a major area for exploration of problems in chemotherapy. About 15 per cent of autopsies show active pyelonephritis and 15 to 20 per cent of patients in the medical wards of the Boston City Hospital have bacteriologic evidence of urinary tract infection despite the use of from one to four antibacterial agents in most of them. Virtually all patients with inlying catheters are found to have bacteriuria. At autopsy more than one-third of patients with bacteriuria have pyelonephritis.

EDWARD H. KASS

Prophylaxis of bacteriuria in patients with inlying catheters has been generally ineffective whether one, two or three drugs are used, undoubtedly because organisms continually are reseeded into the bladder and some of these are inevitably resistant to any drug combination yet devised. Single catheterization is a less formidable procedure because of less opportunity for seeding the bladder; here prophylactic drugs conceivably may be of value; however, direct evidence of this is not at present available.

The rationale for use of drug combinations

*Thorndike Memorial Laboratory and Second and Fourth (Harvard) Medical Services, Boston City Hospital, and the Department of Medicine, Harvard Medical School, Boston, Massachusetts.

in treatment of chronic urinary tract infections has been twofold: to diminish the rate of emergence of resistant mutants, and to broaden the therapeutic range of the drugs either by synergistic action or by simply attacking a greater variety of bacterial species. Inhibition of mutation occasionally may be relevant, but more often the failure of chemotherapy in chronic urinary tract infection is due to implantation of resistant strains and not to production of mutants *in situ*. Pragmatically the use of combinations has not improved the ultimate bacteriologic outcome significantly over the use of single drugs.

A sustained attack on the epidemiologic and individual biologic features of infections of the urinary tract may offer some hope. Present-day approaches have thus far been notably unsuccessful in the management of most chronic urinary tract infections.

Combined Action of Penicillin and Streptomycin in Enterococcal Endocarditis

RALPH R. TOMPSETT*

ENTEROCOCCI found as the infective microorganisms in patients with bacterial endocarditis are highly resistant to penicillin in vitro and their resistance to streptomycin is moderate to high. Although a few patients with enterococcal endocarditis have been cured with penicillin, treatment with this drug alone has generally failed. Only a few patients have been treated with streptomycin alone and here also the results have been poor. Streptomycin alone has generally failed to effect a cure and, moreover, streptomycin-resistant strains of enterococci have emerged in a number of instances.

RALPH R. TOMPSETT

Hunter in 1947 first reported the effectiveness of concurrent administration of penicillin and streptomycin to a patient with enterococcal endocarditis, and subsequent experience has confirmed it. To date we have treated 18 patients in this manner, with 14 bacteriologic cures. Only two patients died of uncontrolled infection, and they received only brief periods of therapy prior to death.

Although the mechanism of the combined action of these drugs on enterococci is not known, in vitro studies have yielded information which may be pertinent: (1) Penicillin may act to prevent the emergence of streptomycin resistance; (2) "persisters" remaining after penicillin has acted may have been rendered highly susceptible to streptomycin; (3) the two drugs together cause more rapid and complete killing than either alone.

The concurrent administration of penicillin and streptomycin (or dihydrostreptomycin) appears, therefore, to represent an example of a therapeutic effect obtainable with two drugs which is difficult or impossible to obtain with either drug alone. However, knowledge of the mechanism of combined drug action does not yet permit any conclusions on the principles which serve as a guide in assessing the combined action of other drugs in other infections.

*Associate Professor of Medicine, Cornell University Medical College; Second (Cornell) Medical Division, Bellevue Hospital, New York, New York.

Combination Antibiotic Therapy of Brucellosis

JOHN H. KILLOUGH*

JOHN H. KILLOUGH

OVER a period of five years, 124 patients with brucellosis were studied for their response to various treatment regimens. In 90 per cent, blood cultures were positive for *Brucella melitensis;* all had agglutination titers of 1:160 or more and compatible supporting data.

The broad-spectrum antibiotics were given in dosages calculated on a weight basis—approximately 2 to 3 gm. daily. For the group receiving oxytetracycline for six weeks the dosage was reduced to an average of 1.3 gm. daily on the fourth day of treatment. Streptomycin was given in 1 gm. doses daily. Cortisone dosage was generally reduced to 100 mg. daily after the first day. Table 1 summarizes the results.

A prolonged course of a single antibiotic in low dosage seemed to be as effective as a somewhat shorter course of two antibiotics with synergistic action. On the basis of previous studies by others we felt that the factor which expresses itself through time is that of host resistance aided by bacteriostasis.

The frequent intercellular position of *Brucella* organisms noted in experimental studies is a peculiar aspect of the infection, and various animal studies have demonstrated that the intercellular position may give protection from antibiotics.

In the present state of our knowledge of pathogenesis and host resistance to this infection one cannot rationalize the different results obtained with different treatment methods.

Either chloramphenicol, chlortetracycline or oxytetracycline alone is very effective in producing an immediate therapeutic response. Unless excessively prolonged, however, single antibiotic therapy leads to a high relapse rate. The present series demonstrated that results with the combination of oxytetracycline and streptomycin are greatly improved over those obtained with either antibiotic alone.

*Department of Medicine, University of Missouri Medical Center, Columbia, Missouri.

TABLE 1

COMBINATION ANTIBIOTIC THERAPY OF BRUCELLOSIS

TREATMENT SCHEDULE	NUMBER	DEFINITE RELAPSE			
		Bacterial with or without clinical	*Clinical without bacterial*	*Total*	
				Number	Per cent
Oxytetracycline, chlortetracycline or chloramphenicol (12 days)	39	26	4	30	77
Oxytetracycline and streptomycin (3 weeks)	22	3	1	4	18
Oxytetracycline and streptomycin (3 weeks) and cortisone (3 to 7 days)	22	1	4	5	23
Oxytetracycline, streptomycin and cortisone (3 weeks)	21	2	4	6	29
Oxytetracycline (6 weeks)	20	2	0	2	10

Antibiotic Combination Therapy of Infected Dermatoses

J. FRED MULLINS*

J. FRED MULLINS

COMBINATIONS of novobiocin and penicillin and novobiocin and tetracycline were utilized in treatment of pyogenic infections of the skin. The various diagnoses included the primary pyodermas, impetiginized dermatitis, and several cases of acne vulgaris. In each case cultures were taken in the usual manner before institution of therapy and all organisms were identified. The majority of patients received a dosage combination of 250 mg. three times daily but some were given up to 500 mg. three times daily. Duration of therapy was from 1 to 68 days.

Tetracycline-novobiocin produced excellent results in 12 cases, good results in four and no results in two. In the more acute pyodermas the responses were observed in three to seven days, whereas the chronic lesions required longer periods for cure. Dosages higher than 250 mg. four times daily were warranted in only a few cases.

Penicillin-novobiocin gave excellent results in seven cases, good results in five, and only a fair response in one. The usual dosage was 250 mg. three times daily and in one instance therapy was continued for 68 days. There were two reactions in this group, appearing on the eighth and the ninth days, respectively; one of the reactions was quite severe, requiring hospitalization of the patient, but it cleared in five days.

Although it is not definitely proved, it has become apparent in the past few years that it might be wise to combine certain antibiotics to obtain a broader, more lethal spectrum of activity and therefore possibly reduce the number of resistant strains. It is also worthy of note that in these 32 cases there was no evidence of gastrointestinal distress, diarrhea or complicating moniliasis.

*Professor and Chairman, Department of Dermatology, University of Texas Medical Branch, Galveston, Texas.

Multiple Antibiotic Therapy of Staphylococcal Infection

LOWELL A. RANTZ*

LABORATORY evidence suggests that combinations of antibiotics may be more effective in inhibiting and killing staphylococci than individual drugs, but attempts to establish their value in treatment of patients have been unrewarding. It has proved impossible to gain useful information in treatment of local, dermal staphylococcal disease because these infections are self-limited after drainage is established.

In order to determine whether the enhanced efficacy of combined therapy could be established, I analyzed data from 24 cases of bacteremic staphylococcal disease. Fourteen of

*Professor of Medicine, Stanford University School of Medicine, San Francisco, California.

the patients had died. All 14 had infection with penicillin-resistant staphylococci, and in nine cases the staphylococci were also resistant to many other agents. The eight patients who had endocarditis all had lived long enough to benefit from effective treatment, but unfortunately two did not receive any antimicrobic therapy, two were inadequately treated, and only four received combined therapy. In two of the latter cases the valve was apparently sterile at autopsy, and in the other two it was not; in all four, serious difficulties in the form of rupture of a heart valve or a ball valve thrombus supervened and the patients died as a result of these mechanical disturbances.

LOWELL A. RANTZ

Among the group without endocarditis, four patients died untreated and two received the wrong treatment. Only five of these 14 patients, in whom the most critical observations might have been made, received combined therapy.

The group of 10 patients who recovered included three cases of endocarditis, and the etiologic agent in four of the 10 cases was a penicillin-sensitive *Staphylococcus*. Several received combined therapy but a good result might well have been attained without it. Three additional patients in whom organisms resistant to several antimicrobic agents were responsible for the infection recovered rapidly after surgical drainage of a local focus, and it was not apparent that the course of the illness was affected by antibiotic therapy.

Only three patients infected by penicillin-resistant organisms were treated with multiple antibiotics without surgical intervention. In one it is probable that the associated use of streptomycin prevented the development of erythromycin resistance, and in another these two drugs effected a cure of vertebral osteomyelitis. Potentiation and suppression of resistant forms in this case were likely.

These observations did not establish that combined antimicrobic therapy of staphylococcal disease is more effective than use of single agents. There were evident discrepancies between the bactericidal effect of combinations in vitro and the clinical results. Mechanical and technical difficulties prevented the satisfactory treatment of many patients. It is doubtful that it will be possible to learn by clinical study whether or not multiple antimicrobic therapy of staphylococcal infection has value.

Clinical Application of Antibiotic Combinations

HARRY M. ROBINSON, JR.*

THERE are relatively few specific indications for antibiotic therapy in the realm of dermatology. These drugs are of value on topical application in treatment of superficial pyodermas. Systemically they should be used only in management of deep pyogenic infections and granuloma inguinale, as adjunctive therapy in acne vulgaris and acne conglobota, and in combination with steroids in severe erythema multiforme.

Recent studies at the University of Maryland have indicated that a combination of an antibiotic with a systemically administered steroid such as cortisone, hydrocortisone, prednisone or prednisolone produces more rapid and lasting involution of lesions of erythema multiforme.

A number of workers have been enthusias-

*Professor of Dermatology, University of Maryland School of Medicine, Baltimore, Maryland.

tic about the results of treatment of acne vulgaris and acne conglobata with broad-spectrum antibiotics; almost all observers agree that penicillin is the least effective in these conditions. It is interesting that after involution of acne lesions is attained by use of broad-spectrum antibiotics a satisfactory result may be retained with a subtherapeutic dosage schedule such as a single 250 mg. capsule daily of the selected antibiotic. Unfortunately when the drugs are discontinued the eruption promptly reappears.

HARRY M. ROBINSON, JR.

In treatment of pyogenic infections requiring systemic antibiotic therapy, the choice of drug is important. The constantly changing nature of the bacterial population and the emergence of resistant strains emphasize the need for routine cultures and for employment of the disk and tube sensitivity tests. Doses must be large enough and treatment continued long enough to completely eradicate the infection. Relapses have been frequent in cases of furunculosis and hidradenitis suppurativa when the period of treatment has not been sufficient.

Statistics compiled on treatment of patients with antibiotics over the past 10 years indicate that penicillin is no longer of much value in staphylococcal infections. Clinical observation and also disk and tube sensitivity tests support this statement.

Numerous organisms either are refractory to antibiotics in their natural state or develop resistance on continued or repeated exposure to a chemotherapeutic agent. Apparently certain combinations of antibiotics are more effective against the refractory organisms than either antibiotic alone. Theoretically, when resistance develops, an initially sensitive strain has undergone mutational change, permitting it to resist the action of a single agent. Therefore it has been postulated that a combination may delay the emergence of refractory strains more effectively than a single antibiotic agent.

There has been a recent trend on the part of research departments of some pharmaceutical companies to develop combinations of antibiotics for treatment of local and systemic resistant bacterial infections. Disk and tube sensitivity tests have demonstrated that these prefabricated combinations are seldom the selections necessary because refractory strains present a variety of resistance patterns. Evaluation of the prefabricated combinations is difficult and the physician should be encouraged to make use of available laboratory facilities and to develop his own combinations of antibiotics to suit individual cases.

There is no clinical evidence to support the theory that a combination antibiotic ointment is necessary for topical therapy. Clinical research has demonstrated that the vast majority of superficial pyogenic infections will respond to single antibiotic ointments.

Clinical Therapeutic Studies of Antibiotic Combinations

WILFRED F. JONES, JR.*

CONTROLLED observations were made on the antibacterial property of the blood of normal persons to whom antibiotics had been administered singly and in combinations. Each subject was given, on separate occasions, a dose of a combination of two antibiotics; an equal dose, by weight, of one of these antibiotics

*Thorndike Memorial Laboratory and Second and Fourth (Harvard) Medical Services, Boston City Hospital, and the Department of Medicine, Harvard Medical School, Boston, Massachusetts.

alone; and an equal dose of the other antibiotic alone.

WILFRED F. JONES, JR.

The drugs were given by mouth one-half hour before breakfast and citrated venous blood specimens were obtained at specified intervals afterward. In each instance the antibacterial activity of the plasma was assayed by a twofold dilution method in broth, using standard test organisms, usually *Streptococcus 98* and *Staphylococcus 209P*. The results from different doses were compared as to the shape of the blood level curves, "total activity" as measured by the area under these curves, and the magnitude of peak levels achieved.

The antibiotic pairs studied, the ratio of the individual components in the combinations, and the total doses employed were as follows: (1) penicillin V, erythromycin, and 1:2 combination, 375 mg.; (2) penicillin G, erythromycin, and 1:1 combination, 500 mg.; (3) penicillin G, oleandomycin, and 1:2 combination, 250 mg.; (4) penicillin G, oleandomycin, and 1:3 and 3:2 combinations, 1000 mg.; and (5) penicillin V, tetracycline, and 1:1 combination, 500 mg. and 1000 mg.

In each instance penicillin yielded greater plasma antibacterial activity than the other agent of the pair, and an equal total dose of the combination of the two agents tended to result in intermediate activity.

Clinical Studies of Antibiotics in Combination

GEORGE GEE JACKSON*

Two theoretical clinical uses for combinations of antibiotics are to increase the number of genera effectively inhibited and to suppress the emergence of resistant strains.

GEORGE GEE JACKSON

We conducted a study on a group of 72 patients with poliomyelitis in whom tracheostomies had been performed because of respiratory difficulty. Routine tracheal cultures were made, and observations regarding prophylaxis and treatment were related to the antibiotics used.

The trachea became infected in a higher percentage of cases (63 per cent) when the initial culture was negative and treatment was not given than when an antibiotic or a combination of antibiotics was given (33 to 47 per cent). A single broad-spectrum antibiotic was the most effective prophylaxis and better than the same agents combined with one or more other antibiotics.

When the initial culture was positive, the use of antibiotics did not improve the elimination of infection or effect a decrease in the number of genera isolated. In this respect, two limited-spectrum antibiotics were better than the combination of one broad-spectrum and one limited-spectrum antibiotic or a single agent.

Implantation of new genera occurred most frequently when a combination of two antibiotics was given (46 per cent) and less frequently when three antibiotics were given (one as an aerosol) (22 per cent). Implantation of new genera occurred in 26 per cent of cases in which no antibiotics were given.

Two clinical aspects of antibiotic resistance

*Assistant Professor of Medicine and Preventive Medicine, University of Illinois College of Medicine, Chicago, Illinois.

are (1) emergence of resistant microorganisms from the strain with which the patient is infected and (2) emergence in the community of resistant strains which produce superinfection during treatment. Studies of staphylococcal infections suggest that the former is uncommon for most antibiotics. A combination of two individually effective antibiotics suppresses resistance of this type.

Resistant strains usually are acquired from the environment. Their prevalence is proportional to the use of antibiotics. Combinations of antibiotics effect only a limited and transient suppression of resistant strains in the hospital environment.

In animal protection studies, penicillin and AUREOMYCIN® were combined to produce a synergism or an antagonism. The principal factor was the relative dose of each. A blanket classification of combinations of antibiotics as synergistic or antagonistic is not warranted and fixed-dose ratios are not desirable.

Panel Discussion; Summary

DAVID E. ROGERS*

THE panel members uniformly believed that the majority of acute bacterial infections can be managed effectively by the intelligent use of single antimicrobic drugs. They agreed, however, that antibiotic combinations have definite advantages in certain well-defined situations, which include the following:

DAVID E. ROGERS

1. Treatment of certain specific infections. Evidence was presented to indicate that combinations of antibiotics yield superior therapeutic results in tuberculosis, enterococcal endocarditis, and perhaps brucellosis.

2. To delay the emergence of antibiotic-resistant strains of microorganisms. The panel members agreed that one can delay the emergence of antimicrobic-resistant tubercle bacilli by administering more than one antibiotic agent. It was noted that the emergence of penicillin-resistant microorganisms *during therapy* actually is extremely rare. Drug-resistant variants develop more frequently with the use of streptomycin, erythromycin or novobiocin.

3. To shorten treatment or decrease dose of antibiotics required, or both. The simultaneous use of penicillin and streptomycin appears to permit less prolonged treatment of streptococcal endocarditis. Convincing evidence was presented to indicate that combined tetracycline-streptomycin treatment of brucellosis shortened the period of therapy necessary to prevent relapse. The use of streptomycin with penicillin has permitted the successful treatment of enterococcal endocarditis with smaller amounts of penicillin than when penicillin is used alone.

4. Treatment of superficial infections due to mixed bacterial populations. There was some evidence that combinations of antimicrobic agents of low sensitizing potential which are rarely used systemically (neomycin, bacitracin, polymyxin) are of value in management of different dermatologic infections.

Treatment of a number of bacterial infections is currently unsatisfactory. While all the panel members used combined therapy in treatment of serious staphylococcal infections, certain urinary tract infections, and bacteremias due to enteric microorganisms, they

*Cornell University Medical College, New York, New York.

agreed that there is little or no scientific evidence that this is necessarily appropriate. Combinations were universally used in these situations because of the unwillingness to omit any drugs of possible benefit to seriously ill patients.

The use of prepackaged antimicrobic combinations was considered unwise. All the panelists agreed that such combinations do not allow appropriate manipulation of dose and represent an increased hazard to patients in that a companion antibiotic is used in many clinical situations where it is not indicated.

Although there were some requests for new broad-spectrum drugs, the majority of the panelists believed that new narrow-spectrum agents of high effectiveness against certain specific infections are the drugs needed currently. These include agents effective against many of the enteric bacilli and fungi. The suggestion was also made that agents should be sought which might aid in the management of infection through support of host resistance rather than direct antimicrobic action.

MEETINGS *and Postgraduate Courses*

ALBANY MEDICAL COLLEGE, ALBANY: Postgraduate courses for 1958:

New medical and surgical approaches to cardiovascular disease, January 9-February 13
Adrenal hormone therapy in practice, February 20-March 13
Sex hormones in adolescence and senescence, March 20 and 27
Fevers and infections: Their diagnosis and treatment, April 3-24
Advanced course in interpretation of electrocardiograms, early in January
Clinical correlation of electrocardiograms with disease processes (hospitalized patients), individually arranged
Clinical refresher course, individually arranged
Obstetric-pediatric refresher course for general practitioners, March 19-May 7

For further information, write to: Dr. Frank M. Woolsey, Jr., Associate Dean and Director of Postgraduate Medical Education, Albany Medical College, Albany.

NEW YORK UNIVERSITY-BELLEVUE MEDICAL CENTER POST-GRADUATE MEDICAL SCHOOL, NEW YORK: Postgraduate full-time courses offered during December:

Recent advances in the diagnosis and treatment of poisonings, 2-4
Infertility, 2-4
Surgery of the cornea, 2-6
Endoscopy: Broncho-esophagology and laryngology, 2-14
Pediatric cardiology, 2-6

A part-time, three months' course in gastroscopy and flexible tube esophagoscopy will begin December 2 and will be repeated March 3, 1958. For further information, write to: Office of the Associate Dean, New York University Post-Graduate Medical School, 550 First Avenue, New York 16.

SISTER ELIZABETH KENNY FOUNDATION, MINNEAPOLIS: Postdoctoral scholarships in neuromuscular diseases are available to selected candidates from medical schools in the United States and Canada who are nearing completion of their fellowship training. Awarded annually, these scholarships provide a stipend of from $5000 to $7000, depending on the scholar's qualifications. For further information, write to: Dr. E. J. Huenekens, Medical Director, Sister Elizabeth Kenny Foundation, 2400 Foshay Tower, Minneapolis 2.

UNIVERSITY OF KANSAS SCHOOL OF MEDICINE, KANSAS CITY: Postgraduate courses offered during 1958:

Pulmonary disease clinic, January 13-14
Gastroenterology, January 15-16
Surgery, January 20-23
Radiology and radioactive isotopes, February 10-13
Clinical chemistry, February 17-18
Radiologic physics, February 2-April 6
Histochemistry, June 9-21
Interpretation of electrocardiograms (1) (by correspondence), April 4-October 3
Interpretation of electrocardiograms (2) (by correspondence), May 1-October 30

For further information, write to: Department of Postgraduate Medicine, University of Kansas School of Medicine, Kansas City 12.

UNIVERSITY OF OKLAHOMA MEDICAL CENTER, OKLAHOMA CITY: Postgraduate short courses for 1957-1958:

Problems in pulmonary diseases, December 11
Growth failure, January 8
Urology symposium and C. B. Taylor Lectureship, February 12
Pathogenesis and treatment of anemia, March 12
Anesthesia for the part-time anesthetist, April 9
Pediatric allergy, May 14
Surgical diagnosis and problem clinic, June 11

For further information, write to: Office of Postgraduate Instruction, University of Oklahoma Medical Center, Oklahoma City 4.

UNIVERSITY OF SOUTHERN CALIFORNIA SCHOOL OF MEDICINE, LOS ANGELES: Postgraduate correspondence courses:

Basic home course in electrocardiography, 52 weekly lessons
Advanced home course in electrocardiography, 52 weekly lessons

For further information, write to: Director, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 33.

Psychologic Aspects of Physical Disability

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THE very term "physical disability" in its common usage implies a disturbance that is purely, or at least primarily, physical in nature. It would appear that an individual can have a physical disability in which the mental or psychic disturbances do not warrant primary consideration. Thus, a fracture of the humerus, an inflamed gallbladder, housemaid's knee or a rheumatic heart may be seen as essentially a physical disability, and the patient is treated by alleviating or eliminating what is considered the apparent physical cause or effect.

At times the physician completely ignores the extent to which such bodily disturbances may be reflected in the patient's cognitive and emotional life, or, if he recognizes it at all, his reaction is to pat the patient on the shoulder and suggest that he "keep his chin up." In short, the doctor is thinking, if not saying aloud, "Stop making such a fuss. You are in my hands. I'll put you back in good physical shape, *ergo* what are you worrying about?"

It is unlikely that the well-trained physician is unaware of the psychologic concomitants which are intimately associated with bodily illness. It is not ignorance of the relationship between mind and body that leads to such a cavalier attitude toward the patient's psychic difficulties, but rather a lack of ideas of what to do about them. The medical man generally knows how to correct or alleviate the bodily ills but often is at a loss in coping with the emotional disturbances, so he either ignores them or tries to make the patient believe they are insignificant. The frequency with which the practitioner discourages the patient from discussing anything but symptoms or signs closely associated with his disability illustrates this clearly. When it comes to the patient's worries, uncertainties or fears, the doctor is very likely to dismiss them with such mundane and ineffective advice as "Stop worrying" or "Forget it"—as though the patient really can turn off his feelings at a mental faucet.

It is my sincere belief that the physician owes it to himself and his patient to deal with these psychic concomitants of physical disability. I shall discuss a few of the various circumstances in which a more empathic approach will result in a better and more prompt recovery.

Some Fundamental Psychologic Components and Their Control

Let us consider some of the recognized psychologic components associated with physical behavior. These include (1) the psychologic response to physical pain; (2) the effect of homeostatic imbalance resulting from alterations in autonomic nervous system control—as evidenced physiologically in altered cardiac rate and volume, respiratory rate and volume, vascular control, etc.; (3) the social trauma of stigmatization associated with physical and mental disability, deviant behavior, and misinformation regarding the relation of the patient to other persons.

Psychologic response to physical pain—Every person has his own unique capacity to tolerate pain. Pain, except under experimental conditions, is a subjective phenomenon, and it is difficult if not impossible to evaluate its "real" intensity in an individual patient. For certain patients in whom the pain threshold is low, we can assume that pain is experienced as severe and that if it is prolonged it may lead to psychic disturbances much more serious than we would anticipate from experience with similar disabilities in other patients. The tendency to treat these patients as though they are malingerers or seekers of undeserved sympathy often leads the patient to consider the physician cold, callous and indifferent. With this attitude, he often loses confidence in treatment, motivation for recovery is reduced, and disability increases.

Contrary to practice, such a patient deserves special attention. An empathic approach to his intolerance to pain, coupled with clarification of the significance of the experienced pain, appears essential if the patient is not to be made even more sensitive. Encouragement and such alleviation as possible may prevent more severe psychic disturbances.

While no one is in a better position to determine when a patient needs medication or other treatment for pain than his own physician, he must not allow his past experience to becloud his judgment regarding the unique characteristics of a particular case. Pain sensitivity being a unique characteristic, he should give each patient all the psychologic help necessary in achieving a capacity to tolerate his pain.

Alterations in homeostasis related to alterations in autonomic control—There are a great variety of physical disabilities in which disturbances in the autonomic nervous system appear to be basic to the underlying disease. In polio, especially where bulbar involvement is indicated, one is likely to find marked alteration in respiration, temperature control, cardiac rate and volume, and cardiovascular control. It would be strange if such alterations in autonomic control involved only motor elements without correlative change in the emotional elements so closely associated with this dynamic mechanism; indeed, there is no reported evidence that such is the case.

Theoretically, the well-trained physician knows the significance of these relationships concerned with maintenance of homeostasis. But in practice his interest more likely is oriented to the physical aspects and the heroic procedures he must carry out to keep a patient with poliomyelitis alive. It is not too surprising, therefore, that emotional disturbances are often sidetracked or even disregarded. By the time the physician has established the lifesaving program, and has resolved the respiratory, cardiovascular, renal, gastrointestinal problems and the like and applied physiatric attention to weakened and ineffective musculature, there is little opportunity to see the psychic-trees for the physical-forest. But the trees are there just the same, and the patient often is harassed more by worry about family, job and his own self-appraisal than by his many physical problems.

Poliomyelitis in its most severe form admittedly is an extreme example, yet it is a good one, for although the number and varieties of physical problems actually may be fewer in other diseases, nevertheless there appears

to be no better attention to the psychic components. In heart disease, for example, it is more likely that a patient with cardiac decompensation will be studied from the standpoint of functional capacity of the failing heart muscle than in relation to the psychic support required to maintain his motivation to live. The alteration in homeostasis created at least partially by faulty cardiac function is reflected in the increased emotionality of the patient, which may further tax an already weakened heart. Is it not, therefore, fully as important to supply psychic support as it is to provide support for the failing heart muscle or to regulate therapeutically the decompensating cardiac conduction mechanism?

The physician who recognizes the importance of the psychologic component in physical disability can do a great deal provided he removes it from the realm of the theoretical and applies this knowledge as a therapeutic guide. A patient with known direct or indirect involvement of the autonomic nervous system may be suffering from both physical and psychologic trauma. Treatment, therefore, should be designed to correct or reduce the mental components as well as the physical. Overlooking the psychologic factors may prove as harmful as failure to treat the physical disease properly.

Application of effective psychotherapy may enhance recovery. Even when complete recovery is unlikely, such psychologic assistance will do a great deal toward preventing more serious mental illness and further disability. As a result, many of these patients may tolerate their physical difficulties much better and may be able to progress toward rehabilitation with more interest and cooperation.

Psychologic factors in immobilization—The psychologic effect of immobility is another area of disturbance which is often either disregarded or greatly underestimated as a factor in physical disability. It is an interesting observation that physicians who themselves cannot remain immobile for 24 hours with equanimity often commit patients to days, weeks, months and even years of confinement to bed without recognizing the probable effect of such a program.

Modern therapeutic concepts and practice have done a great deal toward getting the patient with potential ambulatory capacity back on his feet as soon as circumstances permit. But there are many whose ability to ambulate is minimal and who may be restricted to bed permanently or for long periods. Such patients lose one means of emotional relief that is fundamental to many persons. Most of us are so accustomed to moving about freely and without restriction that we overlook the value of movement as a release mechanism for pent-up emotion. Consider, if you will, the speaker and his gestures; the unhappy, frustrated individual who vents his pent-up feelings by kicking a tin can; and the restless soul who rolls and tosses while trying to fall asleep. These are but a few simple examples of how unhampered ability to move tends to relieve the disturbed psyche.

When restriction of bodily movement cannot be avoided or when the patient's best interest demands serious curtailment of activity, it would seem incumbent on the physician to prescribe compensatory emotional drainage to guard against the dangers of emotional blockage. Clinically, one may encounter examples of failure to recognize the importance of this factor—for example, prior to the days of modern chemotherapeutics, patients with tuberculosis often were confined to bed for many months while they "cured." At times it was overlooked that a number of these patients failed to make the progress anticipated under the prescribed "bed rest regimen" and that their illness ran a prolonged course, with behavioral evidence of psychic disturbances more often than not associated with signs of extension of their disease.

An authoritarian and doctrinaire approach to such patients may bring physical compliance with directions, but it cannot result in the mental relaxation essential to the establishment of a true "resting state." Such enforced restriction of movement may put the body at rest superficially but will not remove or prevent the tensions associated with frustrations, anxiety and aggressive reaction which the patient feels toward himself and others whom he holds responsible for his troubles.

As a rule, such patients would accept restricted mobility more satisfactorily if physicians would help them reduce their emotional difficulties. Such a procedure would call for (1) provision of adequate psychologic support through intelligent use of a medical or a psychiatric social worker who can bring to the patient understanding and empathy and in addition is prepared to take steps toward resolving the more serious problems that trouble him because he is no longer ambulant and cannot act for himself; (2) providing adequate professional personnel augmented by properly trained volunteers to aid the patient in attaining emotional outlets through conversation, constructive learning experiences, and vicarious activities (books, TV, radio); (3) a more understanding appraisal by the physician of the amount of restriction necessary. The limitations on the patient's activity are at times unnecessary, cruel and even harmful. Limitation in activity should be looked on as a fundamental therapeutic process and, as such, should not be prescribed haphazardly or indifferently any more than one would suddenly reintroduce free motion in a limb that had been immobilized for a long time. The physician should be fully cognizant that ability to move about is of great concern to the patient, and therefore that care and consideration in planning reduction or curtailment of motion will frequently yield greater cooperation and satisfaction. Permission to expend some extra ergs of energy at the right time and in the right manner may spell the difference between a patient with high morale who is eager to recover and one who is bitter and depressed.

Effects of stigmatization—Finally, the stigmatization frequently associated with bodily distortion and physical limitation is a serious problem affecting the psychologic health of the disabled patient. Many disabled individuals do not conform with established social standards. Even the less obviously limited patient may suffer socially simply because he cannot maintain the pace demanded by his social milieu.

Stigmatization is a psychologic traumatic process which all too often is recognized by the physician and then promptly ignored. The "nothing can be done about it" attitude so often applied to this problem ought to be corrected. A great deal can be done about it, and it should be of considerable concern to the physician. Two possible approaches to the resolution of this vicious attack on the disabled are worth considering. The first is a long, slow process involving the education of society in the direction of a better understanding of the disabled person, emphasizing his positive values rather than his limitations. Such a program should and often does call for the physician's cooperation in the educational planning; but, in the last analysis, because of limited time, it is seldom the area in which he can make his primary contribution.

The second approach is through proper preparation of the patient toward self-acceptance, self-appreciation and an understanding of how he can demonstrate his own stock of assets. This concept is really fundamental to any effective program of rehabilitation. It should begin with adequate evaluation of the patient shortly after admission to a treatment program. Whether the patient is treated at home, in a hospital or in any other treatment facility, provision should be made not only for evaluation of his physical status, including a functional interpretation of his disability, but also for orientation with regard to how he can work around his limitations and use his intact skills and capacities. The patient should be helped to appreciate that his treatment program not only aims at alleviating pain or correcting deformity or disease, but also includes training in the use of his untapped abilities and skills.

The patient's motivational reservoir can be conserved by *prompt* and *competent* attention to his needs from the onset of his illness. Some patients, especially those with limited motivation to begin with, often lose what little urge they have to do something for themselves simply because they are allowed to sit about or lie on their beds like vegetables for long days or weeks while their physical problems are resolved. This approach leads to feelings of worthlessness and dependence which, once established, are difficult and at times impos-

sible to overcome. Their prevention calls only for the application on a realistic basis of the very fundamentals of the modern rehabilitation concept. The difficulty in attaining this goal often lies in failure to provide competently trained and organized rehabilitation teams in many of our general hospitals. Even fewer such services exist for the home-care patient. The physician as an individual and through his county, state and national medical organizations can encourage the development of good rehabilitation programs wherever he is engaged in practice.

A further step in this direction is to provide training opportunities during hospitalization and afterward so that the patient may learn how to utilize his physical and mental capacities effectively. This calls for good psychologic appraisal to the end that he will be properly oriented toward activities that will satisfy his own ego-needs and in turn be prepared to accept his role in a socio-economic program that will lead him toward independent action and personal security.

Stigmatization is based mainly on prejudice (unsupported and unwarranted opinion) and preconceived notions of how the patient's disability removes him from the "stream of life." Anything that can be done to prepare the patient to counter these false concepts by demonstrating that his behavior is altogether the reverse of these false notions will help him overcome their effects. The prejudiced do not base their views on fact, and there are certain to be times when disabled persons arbitrarily will be denied the opportunity to demonstrate their actual ability. Therefore, it would be desirable to train patients to tolerate such attitudes and to seek the less prejudiced and the unprejudiced who will allow them at least a measurable chance to show what they can do. Nor can we afford to overlook the fact that even the most prejudiced may relax their attitudes when the demand for services or skills exceeds the supply. The extensive wartime employment of the disabled speaks volumes on the verity of this observation. To keep the disabled ready, willing and able to demonstrate their abilities is the morale-building and morale-supporting task of medical personnel.

The use of a variety of technics designed to prepare the patient for many of the negative attitudes he may encounter will help. For example, adaptations of psychodrama, group psychotherapy and counseling programs conducted by competent medical or psychiatric social workers, psychologists, psychiatrists and others can provide a fertile source of help for the patient who cannot handle his emotional reactions unless he has had the opportunity to prepare himself for the onslaught.

A planned program of vocational counseling introduced early in the patient's treatment plan will provide him with a sense of hope and courage and help utilize time that might otherwise lead to psychic, self-destructive inactivity. Successful rehabilitation will include adequate provision of mentally healthy and ego-satisfying experiences.

The Ultimate Solution

There are no more absolute solutions to the psychologic problems than there are for many of the physical ones. Perhaps the best we can hope for is the continuing development of well-rounded rehabilitation programs for all general hospitals of size sufficient to support them. This may be further augmented by rehabilitation centers within one or several communities where individual hospitals are financially unable to support a program on their own. Such outpatient services may then be extended for the home-bound and the home-convalescent patients.

With increased understanding, physicians may be expected to provide adequate support for the patients' ego-structure. This will lead to their better preparation in coping with functional disability and at the same time allow them to make optimum use of their untapped psychologic and physical resources.

The physician's scientific background affords freedom from prejudice and guilt with regard to a patient's disability, and this freedom can help him to explain intelligently the attitudes of others so that the patient will be aware of them and prepared to cope with them. In this area the physician should also keep in mind that before the onset of his illness the patient himself may have had a set of preju-

dices toward disability. Generally these attitudes persist on an unconscious level so that the patient often projects his own dislike of the disabled onto himself and may, therefore, read these projections into the behavior of others when they truly represent his own views. Such a patient needs help in developing insightful appreciation of this behavior. The physician may find that in some instances other colleagues on the rehabilitation team can help the patient understand himself. He should not hesitate to request help from the social worker, psychiatrist or psychologist staff members whenever needed. When such assistance is not available, local social and clinical facilities offering such services should be utilized when feasible.

As understanding and appreciation of the patient increase and as personnel are trained and adequate facilities for rehabilitation provided, we may look forward to great gains in the psychologic care of the physically disabled. This will redound favorably to patients and physicians alike.

MEETINGS *and Postgraduate Courses*

AMERICAN COLLEGE OF SURGEONS: Sectional meetings for 1958:
Dallas, January 9-11
Jackson, Mississippi, January 16-18
New York City, March 3-6
Salt Lake City, March 17-19
Des Moines, March 27-29
Stockholm, Sweden, July 2-7
Chicago, 44th annual clinical congress, October 6-10
For further information, write to: Dr. H. Prather Saunders, Associate Director, American College of Surgeons, 40 East Erie Street, Chicago 11.

HIGHLAND VIEW HOSPITAL, CLEVELAND: Six month postgraduate course in physical medicine and rehabilitation, January 6-June 27, 1958, offered in affiliation with Western Reserve University. For further information, write to: Dr. Mieczyslaw Peszczynski, Chief, Department of Physical Medicine and Rehabilitation, Highland View Cuyahoga County Hospital, Harvard Road, Cleveland 22.

NEW YORK UNIVERSITY POST-GRADUATE MEDICAL SCHOOL, NEW YORK: An intensive course in radioactive isotopes is being offered for the first time by the department of radiology. Designed to be of special interest to internists, radiologists and hematologists, the course may be entered the first of any month during the academic year. For further information, write to: Office of the Associate Dean, New York University Post-Graduate Medical School, 550 First Avenue, New York 16.

THE AMERICAN FOUNDATION FOR ALLERGIC DISEASES, NEW YORK: Two year postdoctoral fellowships in research and clinical allergy are available to selected candidates of approved medical schools who have completed one or two years of graduate training required as a preliminary to certification by the Boards of Internal Medicine or Pediatrics. These fellowships provide a stipend of $4500 for the first year and $4,750 for the second year, with $750 for laboratory and travel expenses during the two year period. For further information, write to: Dr. Colin M. MacLeod, Professor of Research Medicine, University of Pennsylvania, 820 Maloney Clinic, 36th and Spruce Streets, Philadelphia 4; or Dr. Herman N. Eisen, Professor of Medicine (Dermatology), Washington University School of Medicine, 600 South Kingshighway, St. Louis 10.

UNIVERSITY OF MINNESOTA, MINNEAPOLIS: Courses to be presented at the Center for Continuation Study, 1957 and 1958:
Fractures for general physicians, December 5-7
Ophthalmology for specialists, January 6-11
The newer drugs in general practice, January 9-11
For further information, write to: Director, Department of Continuation Medical Education, 1342 Mayo Memorial Building, University of Minnesota, Minneapolis 14.

UNIVERSITY OF TEXAS SOUTHWESTERN MEDICAL SCHOOL, DALLAS: Postgraduate courses offered during 1958:
Surgery (the G.I. tract), April 17-19
Obstetrics and gynecology, May 12-14
Pulmonary diseases (Mattson seminar), June 9-10
For further information, write to: Dr. John S. Chapman, Assistant Dean for Postgraduate Education, 5323 Harry Hines Boulevard, Dallas 19.

YALE UNIVERSITY SCHOOL OF MEDICINE, NEW HAVEN: Postgraduate courses offered during 1958 in cooperation with Grace-New Haven Community Hospital and the Connecticut State Medical Society:
Diagnosis and management of cardiopulmonary disease, January-February, eight weekly sessions
Basic psychiatry, January 6-March 3
Child psychiatry, January 29-February 12 and February 19-March 5
Pediatric neurology, January 8-22
For further information, write to: Dr. Arthur Ebbert, Jr., Assistant Dean of Postgraduate Medical Education, 333 Cedar Street, New Haven 11.

CLINICOPATHOLOGIC CONFERENCE

Report From Veterans Administration Hospital, Hines, Illinois

Report of Case

DR. LEONARD BRESSLER (senior resident, general surgery): A 24 year old white man was admitted to Hines Veterans Administration Hospital on November 13, 1956, with complaints referable to the abdomen. For a month prior to admission he had experienced mild abdominal cramps not associated with meals or any food. There had not been any changes in bowel or urine. Ten hours before admission he had generalized abdominal pain of acute onset, which he described by saying, "I could hardly catch my breath." His physician advised hospitalization. A few hours after the attack of pain he vomited greenish material twice and felt better. The day before admission, he had a small normal bowel movement with the passage of some gas, but the day he was admitted to the hospital he did not pass any stool or gas. He had not had chills, fever or jaundice either during the most recent episode of abdominal pain or with the mild cramps.

History—Appendectomy was performed when the patient was seven years old, following an attack of "acute appendicitis." He had two other episodes of severe abdominal pain, one about a year before admission (October 1955) and one in July 1956, four months before admission. X-rays taken during the first episode at another hospital revealed "partial internal obstruction," and films made during the second episode showed the presence of "spastic something."

Hematemesis did not occur at any time, but in January 1956 the patient had one red bowel movement. He stated that there was some relation between the vague abdominal cramps he had experienced during the month prior to admission and the intake of beer and small amounts of alcoholic beverages. He said he had lost 10 lb. in that month.

Physical examination—Temperature was 99.6° F., pulse 96, and blood pressure 158/90. The patient was well developed and well nourished and appeared mildly dehydrated. Positive physical findings were limited to the

abdomen. The abdominal wall was flat, and there was mild generalized tenderness with slight rebound tenderness in the mid-abdomen and mild voluntary spasm of the rectus muscles. Masses were not palpable, and the liver, kidney and spleen were not enlarged. An old healed McBurney surgical scar was noted. Rectal examination revealed good sphincter tone, and no masses or tenderness was noted in the rectum. The stool was brown and did not contain blood. (It would be helpful to know what the bowel sounds were.)

Laboratory data—On the day of admission the white blood cell count was 14,800 (80 polymorphonuclear leukocytes, 13 lymphocytes, 5 monocytes and 2 eosinophils) and the red blood cell count was 4,900,000. Hemoglobin was 15 gm. and the serum amylase was normal. Urinalysis also gave essentially normal findings. Urobilinogen was 0.12 unit per 100 cc. A repeated blood cell count, which I assume was done on the same day, again showed an increased white blood cell count, 14,200 with 88 polymorphonuclear leukocytes and 12 lymphocytes. The red blood cell count was 4,360,000. Hemoglobin was 13 gm. and hematocrit 40 per cent.

An anteroposterior film of the abdomen was normal. An obstructive series disclosed a slight amount of intestinal content in the large bowel and a few slightly distended loops of small bowel containing fluid levels. The impression was that the findings were consistent with ileus. A posteroanterior chest film was normal.

The next day the nonprotein nitrogen was normal, as were the carbon dioxide-combining power and chlorides. The white blood cell count was 13,600 with 84 polymorphonuclear leukocytes. Hemoglobin was 14 gm. Serologic studies were negative. Urinary amylase was again normal. An obstructive x-ray series was repeated and revealed a marked increase in the amount of gas on the right side of the transverse colon and in the hepatic flexure. There also was some increase in gas and fluid levels in the small bowel. Again the impression was that the findings were consistent with ileus, but they appeared more aggravated.

On November 15, two days after admission, the white blood cell count was 12,500 with 79 polymorphonuclear leukocytes. Red blood cell count was 3,740,000; hemoglobin was 11.5 gm.

On November 21, apparently the patient was improved. A gastrointestinal x-ray series showed that barium passed readily through the esophagus into a normal-appearing stomach. The folds of the duodenum were prominent and the bulb was somewhat irritable but otherwise appeared normal. The findings of the gastrointestinal series were considered essentially negative. X-rays of the small bowel were reportedly normal, with no evidence of obstruction or adhesions about the cecum.

Some weeks later, on December 28, total protein was normal and the bleeding and coagulation times were normal. White blood cell count was 7000 with 64 polymorphonuclear leukocytes. Hemoglobin was 14 gm. and hematocrit 44 per cent.

RADIOLOGIST (showing films): There are multiple fluid levels, and the various films are in keeping with paralytic ileus.

DR. BRESSLER: Initially the patient was kept under close observation as a case of "acute abdomen," but under conservative treatment the abdominal pains subsided. The conservative therapy was followed with a view toward future exploratory operation. The work-up was obtained, and when the appendix appeared to be visualized in the gastrointestinal series it was anticipated that the stump of the previously excised appendix would be discovered. On December 31, 1956, exploratory laparotomy was performed under general anesthesia.

Differential Diagnosis

I think the best way to discuss this case is to start with differential diagnosis of acute appendicitis—although I do not think it was acute appendicitis. In cases such as this, one seldom can make a definitive diagnosis except at operation, but we will try, by exclusion, to come up with the most likely one.

This young man had some chronic disease process which had produced rather vague symptoms for about a year. He had abdominal cramps for one month, which would speak for obstruction. However, during the period of mild abdominal cramps he did not vomit or have any change in bowel habits or any ab-

dominal distention. If this were a case of intestinal obstruction, the ileus on admission would have to be secondary, probably, to gangrene, and I doubt that he would have improved on conservative therapy.

The suddenness of the acute pain experienced on the day of admission and the patient's statement that he could not catch his breath suggest some sort of peritoneal irritation which would result if a perforated viscus had sealed off rapidly, as evidenced by lack of abdominal rigidity and only minimal direct abdominal tenderness and rebound tenderness. One sometimes sees this picture in forme fruste ulcer. However, x-rays of the upper gastrointestinal tract were negative. We would like to know whether or not antacids and belladonnalike drugs relieved the pain during the preceding year.

Pancreatitis can give this type of clinical picture, but the amylase was normal. From 10 to 20 per cent of patients with acute pancreatitis may have normal serum amylase in the first 24 to 48 hours after the onset of the acute attack, but usually there is a long history of pancreatic disease so that normal pancreatic tissue has been destroyed and replaced by fibrosis, and an appreciable rise in amylase can no longer occur.

Another possibility would be a renal stone, but urinalysis gave negative findings. Still another condition to be considered is diverticulitis of the colon with formation of an abscess, but again the barium enema study tended to rule this out.

The surgeons expected to find a stump of the appendix, but I doubt that one could see the stump of the appendix on an x-ray after giving a barium enema, as was reported—or at least as long a stump as supposedly was visualized. Appendicitis begins with obstruction of the lumen and goes on either to obliteration of the lumen or to perforation or abscess. Therefore, barium could not enter the stump distal to the point of obstruction. Also, one would expect some localization of pain to the right lower quadrant beneath the McBurney scar with as much ileus as this patient had. Further, Rovsing's sign or any good point tenderness is not mentioned.

Certain features of this case fit in with the diagnosis of regional enteritis. The latter disease is common in the second or third decade of life and a long period of chronicity usually precedes hospitalization. Abdominal colic followed by diffuse pain, as was present here, is common, as is weight loss. In a series of cases of regional enteritis at the Mayo Clinic, 50 per cent of the patients had had appendectomy previously. However, certain features of regional enteritis are absent, including the most common symptom, namely, diarrhea. One would also expect to find some roentgenographic indication of the condition if it had been present this long, specifically either an irregular mucosal pattern or a string sign (Kantor sign). This was not the case. Neither was there a mass, which is noted in about a third of the cases of regional enteritis, and the patient was not anemic.

My impression is that this case represents Meckel's diverticulum. About half of the patients with this condition undergo operation in the first two years of life. However, after that period it manifests itself most commonly at from 25 to 30 years of age, and males are affected three times as often as females. Most cases of Meckel's diverticulum are asymptomatic and are discovered incidentally during a surgical procedure. Patients who have symptoms can be divided into three main clinical groups. The first is the ulcer-type group. Symptoms are secondary to ectopic gastric mucosa within the diverticulum, causing an ulcer, and these patients have pain which frequently is relieved by antacids and may have any of the complications of a gastric or duodenal ulcer. I believe this patient fits into this group. The history includes one red bowel movement, and I believe an ulcer at the base of the diverticulum perforated and sealed off rapidly, similar to a forme fruste ulcer.

The second group of patients with symptomatic Meckel's diverticulum have symptoms that mimic appendicitis. Frequently they give a history of cramping pain for variable periods, similar to this patient, due to obstruction of the neck of the diverticulum. Secretion collects distal to the obstruction and inflammation sets in, which may lead to gangrene, per-

FIGURE 1. Specimen of ileum with diverticulum on the mesenteric border to the left of the specimen. In the eroded portion to the right is a perforation where the ileum adhered to the neck of the diverticulum.

foration or formation of an abscess. The third group are patients with intestinal obstruction, probably due to volvulus, adhesions or intussusception. As you know, in 95 per cent of cases of intussusception in children less than two years of age there is no organic lesion of the bowel to explain the condition. However, in the 5 per cent in which there is an organic lesion, inverted Meckel's diverticulum is the most common cause, and this is one of the best arguments against nonoperative reduction of intussusception by use of a barium enema. As for the diverticulum not being visualized roentgenographically, this is usually the case. Recently we tried to visualize the distal ileum by putting a Harris tube down 48 hours before and then injecting barium through the Harris tube, but the results were quite poor.

My diagnosis, then, would be Meckel's diverticulum, probably with ectopic gastric mucosa and an ulcer which accounted for the previous episode of bloody stool and which, on the day of admission, had perforated and sealed off. Some diverticulitis probably was present also.

Operative Findings

DR. M. E. RUBNITZ (pathologist): Dr. Bressler hit the nail right on the head.

Approximately 18 in. or 45 cm. from the ileocecal valve was a diverticulum about 7 cm. long and 3 cm. at the widest point. The mouth emptied into the ileum at the mesenteric border, a somewhat unusual finding. A loop of ileum adhered at the point where the diverticulum entered the ileum. A gastric type of mucosa was present within the diverticulum. A small ulcer was found in the ileum just distal to the mouth of the diverticulum. It had perforated and sealed off.

Figure 1 is a photograph of the operative specimen. The diverticulum is along the mesenteric border. Figure 2 shows the opened specimen. The mucosa of the diverticulum differs in appearance from that of the ileum. A peptic ulcer was clearly seen at the point where the diverticulum opened into the ileum. On the serosal surface of the other side of the bowel there was perforation with adherence to the adjacent ileum.

This appearance of the diverticulum along the mesenteric border brings up a problem. The statement has been made that Meckel's diverticulum occurs on the antimesenteric border, and if it is not in that position it is not a true Meckel's diverticulum. Some surgeons have contested that statement. A number of years ago, Dr. Alfred Strauss and Dr. Isaac Abt of Chicago said that Meckel's diverticulum can occur in an area other than the antimesenteric border of the intestine.

A photomicrograph of a section of the ulcer showed marked inflammatory response. A photomicrograph of the mucosa of the diverticulum showed gastric mucosa with parietal cells, chief cells and goblet cells.

This is the correlation, which certainly is not difficult in this case, with the history of pain, cramps, acute onset of abdominal pain, vomiting, positive abdominal signs, and then the operative findings of diverticulum, probably Meckel's, lined with gastric mucosa, an ulcer which had developed near the mouth or opening of the diverticulum, and perforation sealed off by an adherent loop of ileum.

DR. BRESSLER: Could this have been a duplication of intestine?

DR. RUBNITZ: It could, but because of the gastric mucosa it is more likely that it was Meckel's diverticulum.

FIGURE 2. Opened specimen. Normal anal mucosa with a peptic ulcer in the neck of the diverticulum and gastric mucosa lining the entire pouch.

Discussion

DR. GILLESBY: Johann Friedrich Meckel of Halle, Germany (1781-1833), first described this condition. It is, of course, a persistent omphalomesenteric duct or vitelline duct. It may persist as a diverticulum, a cyst or a fecal fistula attached to the umbilicus, and it is an embryologic freak. Like any other embryologic situation, it is a result of something that went wrong in utero. As already mentioned, the symptoms are usually noted in infancy. The exact mechanism always has been difficult for me to understand, because Meckel's diverticulum is in the region of the midgut and yet it contains gastric mucosa, pancreatic tissue or duodenal mucosa—which, of course, are in the foregut—and it has been known to contain colonic mucosa—the hindgut. It is rather puzzling to try to figure out how these connections became disorganized.

We have seen a fair number of cases of Meckel's diverticulum. The incidence is 1.8 per cent for males and 0.8 per cent for females. In two cases we found ectopic pancreatic tissue in the diverticulum. The usual location is on the antimesenteric side of the bowel. Some authorities have theorized that if they are on the mesenteric side of the bowel they are not Meckel's diverticula but are duplications of the gut. The gastric mucosa would seem to rule out that point in this case. However, I disagree with Dr. Rubnitz's comment. I have seen duplications of the intestinal tract in children, with gastric mucosa at the end of them. These are rather interesting because the gastric mucosa is cephalad. Frequently these duplications of the small intestine start in the mesentery and run caudad so that they empty into the small bowel in the isoperistaltic direction, and barium will not go back up into the loop, which is in the mesentery of the bowel. Bleeding may occur in these instances, and sometimes these children bleed to death from a gastric ulcer at the base of the duplication of intestine. However, those I have seen were long, from 1 ft. to as much as 6 ft. of duplication of small bowel in the mesentery, running isoperistaltically with the bowel they accompany, so that they cannot be detected by means of x-ray.

The most important point in a case such as this is consideration of the condition. In children it is important to search for Meckel's diverticulum in all cases. They may be within about 10 cm. to 100 cm. of the ileocecal valve. Distance from the valve is by no means constant, but I would say that approximately 18 in. is the usual distance. You will have to look on both sides of the bowel, because it may be on the other side of the mesentery as it was in this case.

In general one should remove a Meckel's diverticulum by elliptic incision in an oblique fashion—in other words, you do not take this ellipse out of the small bowel either longitudinally or transversely but you do it obliquely so that when you close the elliptic opening in the small bowel the points of scarring will be all along the length of the bowel rather than in one spot, where they may lead to stricture later. Tying off the neck of the diverticulum is not enough. Usually the base is fairly broad. In the case described it was rather a goblet. It looked almost like a pear and was a good deal larger than the specimen shown on the screen—almost the size of a Bartlett pear. If you tie off the neck, you do not know whether

or not you are including some gastric mucosa in the ligature, so I think it is best to put a clamp on the base and then inspect the specimen removed quite thoroughly to determine whether or not you have included gastric mucosa. If you have, you must re-excise some tissue around the neck of the diverticulum. Close in two layers, an inner layer of catgut and an outer layer of interrupted cotton or silk. Recovery is rapid.

This case brings up the question of incomplete appendectomy, or, as we call it, appendectomy in two stages. In the past five years we have had four such cases at this hospital, and I personally have seen six cases in which the patient had an appendectomy in that horrible haven, "Elsewhere Hospital," and the dependent portion of the appendix was removed, leaving enough of the appendix embedded in the cecal wall so that later another episode of acute appendicitis can occur. It is, of course, so simple to avoid this, if you just remember that the appendix is at the confluence of the three taeniae of the large bowel and that is the only place it can be. If you take out the appendix where the three taeniae of the large bowel and the longitudinal taeniae of the large bowel meet, there can be very little stump left. This is a sad commentary on some of our confreres who do not know their anatomy as well as they should.

Some three years ago we saw a patient who for 10 years after an appendectomy was considered a neurotic. He had episode after episode of abdominal pain. He had been given everything from aspirin and so on, and no one had felt that he really had an intra-abdominal condition. We finally operated and found an inch and a half of appendix embedded in the wall of the cecum. It contained fecaliths, and it was obvious from the pathologic and microscopic findings that he had had acute appendicitis in the wall of the cecum at least 10 to 15 times during the 10 years when people had been calling him a neurotic.

It is interesting to conjecture as to whether the case on which this report is based was true Meckel's diverticulum or whether it was a duplication in the mesenteric portion, but I think that question is somewhat academic. In either case you have to operate to find out. Diverticula are not going to be diagnosed very often unless physicians bear them in mind constantly and then find them at operation.

I wish to congratulate Dr. Bressler for hitting this as closely as he did.

DR. WILLOUGHBY: I would like to ask Dr. Gillesby if the man's "neurosis" recurred after removal of the cecum.

DR. GILLESBY: No, he was really cured.

DR. RUBNITZ: There was no appendiceal stump in the case reported herein. The appendix had been removed completely.

DR. HURLEY: I would like to ask Dr. Gillesby to comment on the direction of the peristalsis in Meckel's diverticulum.

DR. GILLESBY: As far as I know, it always goes in the direction of the lumen of the small bowel, physiologically. There is no particular problem with peristalsis. The blood vessels to the diverticulum come off the small bowel, usually at the right, but it is fundamental that the blood supply to the diverticulum will be either on one side or on the other of the small bowel, never on both sides. That is another reason why, first and foremost, you have to look at both sides of the small bowel when you are searching for Meckel's diverticulum.

Editorials

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CRITICAL DISEASES

AMONG the unsolved problems of medical science still remain such conditions as muscular dystrophy, leukemia, aplastic anemia, the nephrotic syndrome, parkinsonism, epilepsy, mongolism, cystic fibrosis, multiple sclerosis and several other conditions affecting the nervous system. Believing that progress is encouraged by inventory of knowledge and evaluation of evidence, the editors of POSTGRADUATE MEDICINE have requested investigators of established repute in the study of these conditions to prepare articles surveying all that is known concerning each of them, including the history, the cause, the pathology, the diagnosis, and such facts as have been developed relative to prevention and treatment.

These are desperate diseases, except for epilepsy, progressing usually from their onset to fatality within a relatively short time. Nevertheless some progress is being made from time to time in understanding of the nature of these conditions. Understanding of the trend of the investigations may lead to accentuation of the rate of progress.

MORRIS FISHBEIN

INSTITUTE OF INTERNATIONAL EDUCATION

IF more men and women in all nations had real understanding of the motives and aspirations of the peoples and governments of other nations, some of the divisive conflicts of today's world might have been avoided. Just as the use of nuclear weapons in resolving international dissension becomes increasingly unthinkable, so the strengthening of every conceivable intellectual and cultural tie that can unite mankind becomes increasingly imperative."

These sentences from the report of President Kenneth Holland of the Institute of International Education indicate the motives of this organization. Few people are aware of the work of the Institute or of its long record of service in the international exchange of persons throughout the world. This is its thirty-seventh annual report.

Recently, the Carnegie, Ford and Rockefeller Foundations have made grants for long-range support of the Institute. At present, there are regional offices in Chicago, Denver, Houston and San Francisco through which colleges and universities in the areas concerned are aided with their foreign student programs. A current project is especially designed to facilitate interchange of students in the field of medicine. In 1956 and 1957, 1,088 new students from other countries were placed at colleges and universities in the United States by the Institute of International Education. Adding to this the students who receive renewals and extensions of grants, the total is 2,832. A general scholarship program has been developed for the hundreds of Hungarian refugee students now arriving in the United States. An English language and orientation center for 300 such students was established at Bard College in December 1956.

Working also to aid American students, the Institute has administered a scholarship program for 60 American graduate students in Germany. Fulbright grants were offered to United States students for study in Chili. Through the Institute, several industries, such as the Union Carbide and Carbon Company, are offering grants-in-aid to students from the United States for study abroad in physics, mathematics, chemistry and metallurgy.

The program of the Institute, including conferences on exchange of students, numerous publications on admission and placement of foreign students, and similar projects, constitutes an invaluable addition to the efforts in this field. The annual budget approximates one and a half million dollars, with the income derived from many agencies but principally from the foundations.

Examples of work by the Institute in the health field are the sending of a team of three American public health educators to India to train local personnel in health education; three awards for study in the United States to medical librarians from Brazil, Israel and Korea; and the training of specialists from European and Asiatic countries in various branches of medicine.

MORRIS FISHBEIN

PHYSICIANS' COUNCIL FOR INFORMATION ON CHILD HEALTH, INC.

ABOUT a year has passed since the announcement was made of the formation of the Physicians' Council for Information on Child Health, Inc. (formerly the National Council on Infant and Child Care, Inc.), designed to assist physicians and the public through consultations and commendations in matters involving the health and welfare of children. The council includes 17 pediatricians, representing many universities and medical colleges. Already codes for medical writing and advertising have been adopted. Educational and promotional material will be publicly endorsed. The council will grant insignia or seals of approval to the commercial or other organizations in the field that meet its standards. Special awards are to be given in recognition of exceptional contributions in education on child health. A code for advertising places limitations on claims and endorsements, provides standards for the evaluation of evidence, and emphasizes the responsibility of the physician in prescribing and recommending. The headquarters of this organization are in the New York Academy of Sciences Building, 2 East 63rd Street, New York 21, New York. The available brochures do not indicate how the council is supported in its work.

MORRIS FISHBEIN

MEDICAL LIBRARIES AND THE COPYRIGHT ACT

A new copyright act passed in Great Britain in 1956 became effective June 1, 1957. Special regulations concern the work of teaching and research libraries. The new regulations exempt certain teaching and research libraries, including those concerned with medicine and science, from the provisions of the act as far as the copying of copyright works is concerned where this is done for research, private study, or to supply other libraries. These regulations have long been needed, because those who make abstracts in the field of medi-

cine for publication in various periodicals are continually distressed as to the possibility of having action taken against them for violation of copyright. The clarification of the status of such abstracting has been most important insofar as it applies to Great Britain, and if something similar is not available in the United States it should be taken as a model.

MORRIS FISHBEIN

PRE-EXAMINATION STRAIN

In every university health center, physicians see substantial numbers of students in whom nervous tension and strain develop in the period before and during examinations. Almost everybody has such strain or apprehension before hearings in court, public appearances or even conferences and meetings. In pre-examination strain, the nervous tension may be so great as to diminish the efficiency of study and injure the chance of success in passing the examination. Insomnia and extreme fatigue during the day frequently accompany this condition.

In the University College Student Health Centre in London, about 10 per cent of the students facing major examinations had symptoms of strain. In a typical case, sleeplessness, persistent apprehension during the day, pessimistic thoughts about the examinations, difficulty in retaining and recalling material recently learned, and a growing sense of desperation and hopelessness prevailed. Some students had headaches, nervous indigestion and frequent periods of dropping asleep over textbooks. The main symptoms were anxiety and fear which included both fear of failure and fear of the examination. In some instances, the fear may have progressed to actual panic. A number of students in the University College refused to recognize the relationship between the impending examinations and their symptoms. Incidentally, this type of anxiety cannot be called a psychiatric disturbance, since it promptly disappears once the examination is over. In some instances when students were mentally unstable, the examination seemed to act as a trigger to establish a crisis which had been brewing for some time.

After an experience of seven years with an annual student population of 3400, Dr. Nicolas Malleson,[1] physician in charge of the Student Health Association in the University College of London, recorded four cases of suicide, only one of which was associated with an examination; that was a student who had been mentally disturbed for several years. Incidentally, Dr. Malleson notes that some students who were accustomed to wearing sports jackets and jerseys during their daily attendance in school reported for examinations brushed neatly and squeezed into stiff collars. This he interprets as a recognition by the student that not only is his knowledge in question but also his whole life and character.

In treatment, the establishment of confidence is the prime requisite. Such confidence is established and maintained only by continuous contact with the student up to and through the examination period. Thus, the physician must see the student, if necessary, once a week or even once each day as consultation is needed. Drugs, Dr. Malleson found, are seldom important in treatment, but he has used hypnotics and, occasionally, caffeine or other stimulants. However, he has found that (1) there is no evidence that any drug improves high-grade intellectual performance; (2) anxious students are unreliable; (3) the dosage of sedatives to prevent insomnia must be continually increased; and, finally, (4) a drug should never be given for the first time on the day before or on the day of an examination, because failure then will certainly be blamed on an untoward effect of the doctor's pills.

Scientifically, the Health Centre examined the records of the students who were treated for pre-examination strain, and it was found that their average of passing examinations was the same as that of students of the college in general.

MORRIS FISHBEIN

REFERENCE

1. Malleson, N.: Treatment of pre-examination strain. Brit. M. J. 2:551-554 (September 7) 1957.

NATIONAL NEUROLOGICAL RESEARCH FOUNDATION

AMONG the most baffling illnesses which confront medical investigation today are such neurologic disorders as multiple sclerosis, amyotrophic lateral sclerosis, muscular dystrophy, cerebral palsy, paralysis agitans, epilepsy and senile changes in the brain. With a view to encouraging the attack on these illnesses, the National Neurological Research Foundation has been established, with a distinguished list of philanthropic and professional associates. The honorary president is Dr. Fuller Albright of Harvard; the chairman, the Honorable William Marvel, vice-chancellor of the state of Delaware, and the trustees include such names as Emile F. Du Pont and Mrs. Charles A. Munn, Jr. The Scientific Advisory Committee includes the following:

Raymond D. Adams, M.D., Chief, Neurological Service, Massachusetts General Hospital and Bullard Professor of Neuropathology, Harvard Medical School, Boston

Edward M. Dempsey, Ph.D., Professor and Head of the Department of Anatomy, Washington University School of Medicine, St. Louis

Louis S. Goodman, M.D., Professor of Pharmacology, University of Utah College of Medicine, Salt Lake City

Seymour S. Kety, M.D., Professor of Clinical Physiology, University of Pennsylvania Graduate School of Medicine and Scientific Director, National Institute of Mental Health and National Institute of Neurological Diseases and Blindness, Bethesda

Oliver Lowry, M.D., Dean and Professor of Pharmacology, Washington University School of Medicine, St. Louis

Horace W. Magoun, Ph.D., Professor of Anatomy, University of California School of Medicine at Los Angeles

James L. O'Leary, M.D., Ph.D., Professor of Neurology, Washington University School of Medicine, St. Louis

A. Earl Walker, M.D., Professor of Neurologic Surgery, The Johns Hopkins University School of Medicine, Baltimore

In addition, there is a professional advisory committee; undoubtedly, as the organization develops, many other important names will be added.

As evidence of the need for such a foundation, attention is called to the death of Eugene O'Neill from paralysis agitans and of Lou Gehrig and Joyce Cary from amyotrophic lateral sclerosis. Obviously, this list could be tremendously extended. The Foundation proposes to accumulate funds with which to support projects in research and fellowships of from $10,000 to $12,000 yearly for a period of five years. Estimates indicate that neurologic disorders affect 20 million persons in the United States. Cumulatively, these diseases rank third in the list of causes of death and are responsible for disablement of some 10 million persons.

Inquiries and contributions may be sent to the national headquarters at 3255 N Street, N.W., Washington 7, D.C.

MORRIS FISHBEIN

THE RECOVERY ROOM

MORE and more hospitals in the United States are recognizing the value of the recovery room for use in the postoperative period. Dr. William S. Howland[1] of the Memorial Center for Cancer and Allied Diseases in New York has recently stated succinctly the functions of the recovery room.

In the United States, responsibility for this phase of the hospital's work has gradually devolved on the anesthesiologist. Because the recovery room is open 24 hours a day, a resident anesthesiologist in the Memorial Center sleeps in a room adjacent to the recovery area at night. Since the recovery room is adjacent to the operating rooms, one or more physicians are constantly available for consultation, treatment or resuscitation. The primary task is that of the nurses. Dr. Howland believes that nurses should be assigned to the recovery room on a permanent basis, without any additional duties. Sufficient nonprofessional personnel should be available for clerical, transportation and housekeeping duties, so that the nurses may give all of their time to the care of patients. Forms have been de-

veloped for recording the progress of the patient. Here are recorded blood pressure, pulse, respiration, reaction time from anesthesia, intake and output of fluid, time and method of oxygen therapy, and a record of the administration of analgesics, antibiotics or other medications.

The recovery room should be large, not just a little cubicle or partition, so that crowding will not result when a number of persons or a large amount of equipment needs to be assembled at the bed of a patient who requires intensive treatment. "At Memorial Hospital no visitors are allowed in the recovery room. When patients become critically ill they are removed to a specially designated critical room, where they may be visited by their relatives."

Among the special facilities of a recovery room are included bedside equipment for recording blood pressure, an individual oxygen outlet with each bed, and facilities for suctioning fluids from the pharynx, trachea and bronchial tubes. Special beds with removable footboards and headboards to facilitate bronchoscopy or endotracheal intubation for resuscitation and special equipment for the treatment of anesthetic or surgical complications are desirable.

In the experience at Memorial Hospital the most frequent complications requiring treatment in the recovery room are insertion of thoracotomy drainage tubes for tension pneumothorax; suture of bleeding wounds; emergency tracheostomy; treatment of shock, requiring the insertion of a venous catheter; and cardiac arrest. In 1956 there were two cases of coronary occlusion and four of pulmonary edema. In regard to the special equipment that may be required, Dr. Howland states:

> The treatment of respiratory difficulties requires a resuscitator, an automatic respirator, laryngoscopes and endotracheal tubes, and complete bronchoscopic facilities. There should also be readily available a sterile tracheostomy tray and complete tracheostomy fittings for the resuscitator in case artificial respiration is necessary. The treatment of cardiovascular emergencies requires blood and "cut-down" sets with venous catheters for shock; thoracotomy sets for cardiac massage; and an electrocardiograph for the diagnosis of coronary occlusion. Simple facilities should be available for the determination of hematocrits and hemoglobins and urine sugars and acetones.

The advantages of a well-equipped recovery room are so obvious that hospital architects of standing are now likely to include a recovery room in the plans for new hospitals.

MORRIS FISHBEIN

REFERENCE

1. Howland, W. S.: The function of a recovery room. Excerpta Medica (Surgery) April 1957.

POSTGRADUATE MEDICINE HONORED

At the annual session of the American Medical Writers' Association, held recently in St. Louis, Postgraduate Medicine was honored with an unusual distinction. The publishers, the editors and the staff are proud to have this recognition. The citation reads:

> Whereas, Postgraduate Medicine, Charles W. Mayo, B.A., M.D., M.S., F.A.C.S., D.Sc., LL.D., Editor-in-Chief, has been selected as the 1957 recipient of the Honor Award for Distinguished Service in Medical Journalism, Class 1-A, of the American Medical Writers' Association for accuracy, clarity, conciseness and newness of information; for excellence of design, printing and illustrations, and for distinguished service to the medical profession. In Witness Whereof, the seal of the Association and the signatures of the proper officers are hereunto affixed this 27th day of September A.D. 1957.

This citation was signed by Dean F. Smiley, M.D., president; Vincent F. Williams, M.D., chairman, Board of Trustees, and Harold Swanberg, M.D., secretary.

Our contributing editor, Dr. Morris Fishbein, was honored by election to the presidency of the American Medical Writers' Association and Miss Sylvia Covet, executive editor, was re-elected to the Board of Trustees.

All of us wish to express to the American Medical Writers' Association our happiness in the award and our thanks for the citation.